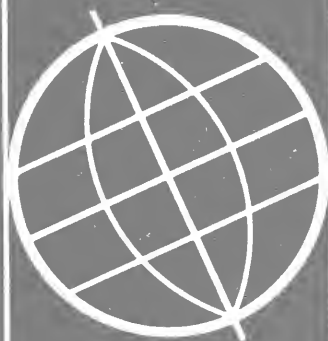


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national institutes of health
**annual
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fiscal year 1978

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

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00 **NATIONAL INSTITUTES OF HEALTH**
ANNUAL REPORT OF INTERNATIONAL ACTIVITIES
FISCAL YEAR 1978

Prepared by
John E. Fogarty International Center
for
Advanced Study in the Health Sciences

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

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Introduction

This is the 10th annual report of the international activities of the National Institutes of Health (NIH) published by the John E. Fogarty International Center for Advanced Study in the Health Sciences. It is a summary, primarily in narrative form, of the highlights of activities for fiscal year (FY) 1978 and is supplemented by two companion booklets, NIH Statistical Reference Book of International Activities and NIH International Awards for Biomedical Research and Research Training.

Over the years of its existence, NIH has been involved extensively with scientists and NIH counterpart organizations of other countries and international organizations in furtherance of its biomedical research mission. The principal legislative authority for the conduct of these international relationships is contained in Section 307 of the Public Health Service Act. International cooperation has made it possible to draw upon particular expertise and experience existing in other countries in addressing the many health and disease problems faced by the United States and the world generally. At the same time, cooperation permits U.S. scientists to broaden their horizons through productive contacts abroad. To the extent that U.S. and foreign biomedical research efforts can be coordinated and resources shared, duplication of effort is avoided and research progress enhanced.

Although we speak in this report of NIH international programs and activities, it is very important to emphasize that these international efforts include not only those of NIH scientists and physicians but also those of universities and research institutions throughout the United States and abroad. These latter activities are conducted using extramural support mechanisms of NIH and its components via research grants, contracts, fellowships, etc. As a consequence, the biomedical community at large is involved, adding strength to the total research, research training and educational capabilities of this and other countries. Through these intramural and extramural means, all components of NIH participate and share to differing degrees in international activities, depending upon their particular needs and missions.

The Fogarty International Center was established in 1968 for the special purpose of fostering a broad and international approach to disease problems and issues and of being a focal point at NIH for coordination of NIH international interests. Its activities, therefore, form the first major subdivision of this report. Activities of other Institutes and

components of NIH which have important international relationships are encompassed in the second major subdivision.

Fiscal Year 1978 was fairly typical among recent years for the level and extensiveness of international activity. Economic conditions and budget limitations naturally precluded undertaking certain research initiatives that would have been desirable. Nevertheless, accomplishments were significant, as discussed herein. In line with overall Government initiatives in international health, increasing attention was given to the potential for mutually valuable relationships with developing countries in a number of scientific fields, such as tropical and infectious diseases. Impossible of recording, of course, is that large and vital segment of international activity which goes on informally directly between individual scientists at meetings, during visits, by correspondence or through exchanges of biological materials. Such contacts form an essential matrix for institutional relationships and in a larger sense are the ultimate goal of more formalized international programs, namely, to make possible, and open, doors of communication.

Questions concerning this report and its companion documents should be addressed to Dr. Joseph R. Quinn, Chief, International Cooperation and Geographic Studies Branch, Fogarty International Center.

Leon Jacobs, Ph.D.
Director
Fogarty International Center

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John E. Fogarty International Center for Advanced Study in The Health Sciences

In recognition of the growing importance of international relationships for the advancement of biomedical knowledge in seeking solutions to the cause, prevention and treatment of disease, the Fogarty International Center (FIC) was established by the Congress in 1968 through Public Law 90-557 as a component of NIH. Some of its functions were incorporated from the former NIH Office of International Research; others were added since its establishment. The Center's name recognizes the staunch support given to biomedical research by the late Congressman John E. Fogarty, who did much to acquaint the public and the Congress in the post-World War II era with the importance of continuing and long-range support of biomedical research for the ultimate amelioration and solutions to disease problems.

The Fogarty International Center serves NIH both as a component with its own particular programs, for which it is uniquely suited, and as a resource for coordination and services for overall NIH international relationships. In these capacities, the Center works closely with other units of the NIH scientific complex on many activities where mutual interests can be served, where subjects cut across the interests of several agencies, or where an issue is of broad concern to NIH as a whole—such as the joint sponsorship of conferences. Indeed, most of the activities of the Center coincide in one way or another with the specific scientific interests of one or more of the NIH components and are mutually supportive, directly or indirectly.

The Center interprets its role with respect to "international" in a very broad way, not only in the more restricted sense of dealing with specific countries and international organizations, but also in terms of dealing with significant issues, problems, or research interests which transcend national boundaries. It is in this way that the Center feels it can best serve both the domestic and international interests of the United States and NIH most effectively.

As detailed in the following sections, the Advanced Study Programs and the International Research Fellowship and Exchange Programs of the Center are activities which are directly administered, and, in most cases, funded by the Center. They may also be jointly sponsored and supported together with other NIH Institutes or outside organizations. In serving its other role of coordination for NIH international relationships, the Center provides staff guidance, oversight, and support for

international interests or activities of NIH as a whole whose final implementation devolves upon the various components of NIH or other organizations.

U.S. Government support for the Gorgas Memorial Laboratory, Panama, through its parent organization, the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., is also included as an activity of the Center. Although the Institute is a private organization, the core support for operation and maintenance of the laboratory is provided through the budget of the Center. The responsibilities of the Center are limited to liaison and general program oversight with respect to these funds.

Finally, because of the scope of these functions and interests, the Center is able to serve the Director of NIH, Institute Directors, and principal staff as an information and advisory resource on international matters.

Advanced Study Programs

The Advanced Study Programs form a key part of the concept and purpose of the Center, serving as important means for the development of biomedical knowledge, acquisition and communication of research information, and the consideration of issues related to the applications of research to the solution of major health problems. These programs draw upon the expertise of U.S. and foreign scientists, administrators, and other specialists for the consideration of various topics of current relevance, many of which require a multidisciplinary approach or bridge the interest of specialties or missions of the categorical Institutes of NIH.

Scientific Meetings

Conference activity at the Fogarty International Center increased in FY 1978 over that of FY 1977 as the Center undertook the management of additional meetings which in the past had been handled by individual lead Institutes. Those conference topics that overlapped the categorical interests of individual Institutes, e.g., as in diabetes research, kidney research, epidemiology, nutrition, toxicology, fundamental research in molecular biology and immunology, etc., were reviewed with appropriate components of NIH and other Federal agencies. Multiagency sponsorship of scientific meetings broadens the participation and scientific coverage, reduces overlap and duplication of efforts, provides for a more extensive scientific review, and spreads the burden of costs.

In FY 1978 there were a total of 91 proposed meetings of which 71 were approved. Funds requested for meetings approved by review exceeded \$1,750,000, of which approximately \$1,300,000 was provided. Of this total, the Fogarty International Center provided about \$500,000,

the remainder being contributed by other agencies. Seventeen of the FY 1978 meetings were held at NIH and 24 took place overseas; this was an increase from four at NIH and eight abroad in FY 1977.

The number of co-supporting agencies participating in the scientific review ranged from 2 to 17 per conference, with the average exceeding 7. The average cost for a conference held at NIH in FY 1978 was \$26,284. Meetings not held at NIH varied in size and location and received an average level of support of \$17,223, with a range of \$2,000 to \$70,000. For these conferences, support for the individual participant was limited to the cost of his or her round-trip transportation at economy rates.

The following meetings were held during FY 1978:

- *National Conference on Clinical Trials Methodology*

Last year there were nearly 800 clinical trials involving NIH. The usefulness of such trials, which frequently involve the participation of physicians and hospitals in many parts of the country, depends on the adherence to a common set of practices and uniform reporting of observations and results. The cooperation and degree of interest of the medical community in this effort was exemplified by the fact that 700 professionals came to NIH at their own expense to participate in the national conference on clinical trials methodology, managed by FIC and sponsored by the NIH Clinical Trials Committee, and 11 of the components of NIH.

The essential consensus that developed at the conference was that a considerable body of information on clinical trials methodology is available, but adequate mechanisms for exchanging this information do not exist. It was proposed that an organization be established which would assess the interests of those working in clinical trials, including the organization of conferences and the sponsorship of a journal that would publish material on clinical trials methodology.

- *Conference on Obesity*

Obesity is one of the major public health problems in the United States; it is estimated that between 30 to 50 million Americans are overweight. More than 100 experts from the United States and abroad gathered at the National Institutes of Health to consider obesity, its problems and treatments, and to recommend courses of action.

Proposals for public action included discussion of ways to better inform physicians, as well as members of the public, regarding the effects of obesity on health and of means of lifetime weight control. The associated increased risks of diabetes, endometrial cancer, stroke, high blood pressure, and heart attacks, not to mention the social and psychological impairments, were discussed.

Conferees expressed particular concern regarding the liquid protein diet because of the possibility of serious side effects, including depletion of potassium. (Subsequently, the Food and Drug Administration im-

posed limitations on the sale of liquid protein diets.) Labeling of caloric and nutritional values of foods was discussed, as well as economic rewards for weight loss, such as reduced insurance premiums.

Priorities for basic and clinical research were agreed upon, and publication of the conference proceedings is in progress.

- *The Biomedical and Behavioral Basis of Clinical Nutrition: A Projection for the 1980's*

The Nutrition Coordinating Committee of NIH, aided by the Fogarty International Center, sponsored this conference to review biomedical and behavioral research in nutrition, to relate this research to current clinical practice, and to project the future frontiers of nutritional investigations and applications.

The conferees considered as a pressing need the encouragement and extension of clinical nutrition research as an essential foundation for continued improvement in man's well-being. They specifically cited the actions of nutrients on certain key regulatory enzymes that govern the disposal of drugs and environmental pollutants, and the different roles of saturated and unsaturated fats on the regulation of cholesterol and lipoprotein metabolism and the consequences in terms of coronary heart disease.

- *The International Workshop on Longevous Population of Vilcabamba, Ecuador*

Vilcabamba was one of three populations renowned for extreme longevity and apparent good health in old age; the other two populations being the Hunzas of Pakistan and the Georgians of Russia. The National Institute on Aging and the Fogarty International Center collaborated in bringing together scientists from six countries who had worked in Vilcabamba.

Prevailing misconceptions about longevity in Vilcabamba were dispelled after a careful construction of family genealogies which showed that the Vilcabamba "centenarian" would be about 86 years old. The initial confusion arose in part from the common custom of giving a surviving child the same name as a sibling who had died. Also, the practice of passing a name from one generation to the next caused confusion in recorded birth dates—the birthday of a grandparent being taken as the birth date of a parent. Consequently, a person's age was often the sum total of more than one family member.

The real scientific import of Vilcabamba was the unusually healthy condition of the elderly who comprised a typical age distribution relative to other populations, but whose incidence of atherosclerosis in people 80 and over was uncommonly low.

- *Colloquium on Selected Diarrheal Diseases of the Young*

International experts on diarrheal diseases of the young were brought together to draft conclusions and recommendations for the control and treatment of these diseases, and to disseminate this information

to the human and veterinary medical communities for the public welfare. Diarrheal diseases of the young are caused by similar pathogens whether "the young" are calves, piglets, or human babies. In man, diarrheal diseases are among the most common diseases experienced, second only to upper respiratory tract diseases, and these diseases are endemic in most developing countries, constituting a life-threatening condition for the newborn.

One widespread cause of diarrhea in human infants and in young animals is the rotavirus. Other common causes of diarrhea include parvoviruses (cat distemper), corona viruses, and a variety of bacteria, including toxigenic and invasive *E. coli*, *Salmonella*, and *Cryptosporidia*. The participants agreed that the newborn succumb to diarrheal diseases, not because of the viral or bacterial agent, but more often because of the loss of electrolytes and water with consequential dehydration, acidosis and shock. Therefore, it was recommended that any program developed to control diarrheal diseases must emphasize preventive measures and supportive treatment.

The majority of scientific meetings sponsored and managed by the Center were devoted to an analysis of recent research results, interpretation of such results contributing to the scientific basis for preventive, palliative, or curative measures. An area of basic research undergoing rapid development, with increasing implications for medicine, is complex carbohydrates in biological recognition, the subject of a conference held in July of 1978.

- *Complex Carbohydrates in Biological Recognition*

Complex carbohydrates play a crucial role in biology by conferring specificity to structures in which they occur. Their presence is manifested in phenomena such as the selective binding of cells of enzymes, hormones, and toxins; the immune response; cellular adhesion; and the control of differentiation and cell growth. This specificity results from the recognition of particular carbohydrate sequences in glycoproteins or glycolipids by complementary sites on proteins. The questions discussed at the conference were how are these specific recognition determinants displayed on complex carbohydrates, and how do the carbohydrate sensors, after perturbation, transmit specific signals.

The consensus of the conferees at the meeting was that the field of complex carbohydrates in biological recognition is at present in an explosive state of development, with increasing implications for medicine, directly involving diverse areas such as enzyme replacement therapy, organ transplants, tumor immunology, protection against infectious disease and toxins, and novel approaches for targeting of drugs.

Other conferences of research interest with significant medical implications held at NIH in FY 1978:

- International Symposium on Papovaviruses and Their Role in Cell Transformation and Oncogenesis

- NIH/WHO Workshop on the Ecology of Influenza Viruses
- Meeting of Committee on Typification of Species of Protozoa
- International Meeting on Guidelines for Detection of Hepatotoxicity Due to Drugs and Chemicals
- Symposium on Autosomal Dominant Genetic Neurological Disorders

During FY 1978 the Center coordinated the limited, partial support of international meetings of topical interest to the mission of the NIH, which included the following research areas: in vitro induction and measurement of antibody synthesis, bacteriology, mycology, biophysics, virology, transplantation, invertebrate pathology, streptococci and streptococcal disease, Raman spectroscopy, flavins and flavoproteins, mononuclear phagocytes, biological membranes, and leukocyte cultures.

Domestic meetings not held at NIH, but of programmatic interest to the Institutes, in which the Fogarty International Center participated, included conferences on: Transmembrane Signaling; Normal and Abnormal Red Cell Membranes; Persistent Viruses; Fast Biochemical Reactions in Solution; Bleomycin; Hemoglobin Synthesis; Theoretical Biology and Biomathematics; Histocompatibility; Bacterial Genetics; Microbial Toxins; Immunochemistry and Immunology; Steroid Receptors; Cell Culture Techniques; Interferon Standards; Alternatives to Insecticide Control; Cell Hybridization; B Lymphocytes in the Immune Response.

Scientific Memoranda

New data are relatively useless until communicated to those who can use them. For the efficient expenditure of research time and money, there should be prompt and extensive communications between research scientists of this and other countries.

Close scrutiny of research endeavor reveals that the most valuable communications are those conducted informally between scientists. Information passed during experiments can help avoid costly errors. Discussion of results at the end of an experiment can pass the beneficial results many months before that same information becomes available through publication of a formal manuscript in scientific journals. Furthermore, informal communications reveal negative results when they occur, and such results often do not appear in the scientific literature.

With these values in mind, the Scientific Memoranda were started as a means for fast, frequent, and informal communications between research investigators. Conducted on a worldwide basis, with participation by scientists anywhere, the Scientific Memoranda enable a rapid flow of informal communications by all researchers in the world interested in the subject of a specific Scientific Memoranda. Current projects, listed below, are sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), the Blood Bank of the Clinical Center, and the Fogarty International Center.

1. Interferon Scientific Memoranda (ISM)
2. Hepatitis Scientific Memoranda (HSM)
3. Leprosy Scientific Memoranda (LSM)
4. Liver Cancer Scientific Memoranda (LCSM)

About 1,500 active investigators located in 48 countries are participating in the Scientific Memoranda.

Research Coordination Projects

The Fogarty International Center coordinates certain projects in which several Institutes have an interest or mission. With its background in international collaboration, FIC also assists the Institutes in initiating and managing special intercountry projects. Some examples are:

1. *Lassa Fever*. Little is known about this serious viral disease, with a very high case-fatality rate, except that it occurs in certain parts of Africa, that it is apparently highly contagious, and that there is no known specific preventive measure or treatment other than hyperimmune serum. On the other hand, it resembles Argentine Hemorrhagic Fever and Bolivian Hemorrhagic Fever. Taking cues from those diseases, a group of scientists concluded that studies should be made of the wild rodents in the area of human Lassa Fever cases. This resulted in a project involving the Center for Disease Control (CDC), NIAID, the Smithsonian Institution, a wildlife studies unit of the University of Colorado, and the proper authorities of Sierra Leone. The project is funded through a contract managed by FIC.

2. *Study of the Influence of Animal Disease Control on the Quality of Human Health*. The theory, often debated, is that efforts to improve disease prevention and control in animals, especially food animals, can have a greater impact on human nutrition and health, employment and standard of living and the economy of a developing country, than any other large undertaking. A 2-year study by Dr. Wilford S. Bailey of Auburn University was reviewed and approved by the Rockefeller Foundation, U.S. Department of Agriculture (USDA), CDC, NIAID, and FIC, and is being funded, in part, by a contract managed by FIC. A segment of the report was presented as a presidential address at the American Society of Tropical Medicine and Hygiene.

3. *Expert Evaluations of Influenza Strains and Outbreaks*. Influenza is a health problem of major concern to all countries. Because of the genetic shifts in influenza strains and

the possibility that new human strains may arise as recombinants of animal or bird strains of influenza viruses, there is a worldwide research effort in this field. International seminars are being held to assess the evolving knowledge from influenza studies, to assure the use of the most up-to-date vaccines, and to plan the most productive research studies. The results will be evaluated at an international workshop and conference.

The 1978 Influenza Evaluation Project was a joint effort of WHO and FIC. In the planning and conduct of this project, scientific advice and sponsorship was provided by CDC, FDA, NIAID, and USDA. Two invited virologists from the People's Republic of China attended.

4. *Study of G6PD Deficiency in Volunteer Subjects.* This enzyme deficiency is a genetic disorder expressed as hemolytic anemia on exposure to oxidant drugs or during infections. Studies have revealed that anti-oxidant drug compounds, including vitamin E, may serve to protect the cells against the oxidant damage.

NIH investigators, Indiana University Hospitals, and Johns Hopkins University Medical School made tentative arrangements with colleagues in Greece to participate in a large-scale clinical trial with patients with this deficiency. The FIC arranged for review and funding of this project in collaboration with the National Institute of Child Health and Human Development (NICHD) and the NIH Clinical Center.

5. *Task Force on Use and Needs for Chimpanzees.* The Endangered Species Act and other forces are cutting off the supply of imported chimpanzees needed for a variety of research studies. An obvious answer is the development of U.S.-based breeding colonies and other resources. The NIH Interagency Primate Steering Committee asked FIC for assistance in approaching this problem. With FIC guidance and management, a task force, including a planning group and appropriate specialists, was selected to prepare a report within 3 months. The report would include the type of studies, the number of chimpanzees needed, and the type of available resources. The project is jointly sponsored by seven NIH components, CDC, National Science Foundation (NSF), and Walter Reed Army Institute of Research (WRAIR).

6. *Risk Assessment of Recombinant DNA Experimentation with E. coli K12.* In the period of worry and concern about the potential hazards and need for control of DNA recombinant research, there was a great desire for a means to

assess the risks. Two NIAID intramural scientists, Dr. Malcolm F. Martin and Dr. Wallace P. Rowe, offered to do the definitive experiments which, if properly designed, would prove the current laboratory models and techniques to be dangerous or otherwise. Drs. Martin and Rowe applied to FIC, and after official review and approval by NIAID and FIC, a task force was launched. After a series of planning meetings with different groups of specialists, an evaluation and consensus development exercise on the subject emerged. That session, known as the Falmouth Workshop, laid to rest many of the worries about DNA research hazards. The report was published as a special supplement to the May 1978 issue of *Journal of Infectious Diseases*.

7. Visit by a Tropical Medicine Group to the People's Republic of China. Stemming from negotiations conducted by the American Society of Tropical Medicine and Hygiene, tentative plans were made for a visit to institutions in the PRC by a U.S. scientific group. FIC developed the support mechanism and management of the project which enabled 21 American scientists to make a very useful visit to the PRC. NIAID, FDA, and CDC helped in the selection of participants.

8. New Tissue Typing Reagents. In the process of tissue typing, originally developed to match compatible organs for transplantation, it was discovered that there is individual and specific group differences in susceptibility and resistance to diseases and disease conditions. A tissue difference in the erythrocytes of certain black populations explained their "natural" resistance to malaria.

Tissue typing experts discover, over a period of time, a number of new tissue specificities that have not been characterized, identified and labeled. When sufficient new unknowns are available, a project is developed to have the new candidates cross-tested against known standards by about 100 testing laboratories over a period of several months. The accumulated testing data from thousands of tests are analyzed by computer and new reagents identified.

With sponsorship from all NIH components and FDA, interested in tissue typing, the FIC developed and managed a supportive contract for the new reagent characterization studies.

Geographic and Policy Studies

During the 10 years of its existence, the Center has initiated and supported a number of studies by U.S. and foreign experts on topics of

current concern and interest to the health and scientific communities. These generally result in monographs published by the Center, or in some instances through other publishers, such as scientific journals. Many of the studies have been of a geographic nature, concerned with various aspects of health services and research in certain other countries. Others have been analyses of health policies as viewed from international perspectives.

The nature of these studies is constantly evolving in accordance with emerging needs and interests. Indeed, the Center attempts to anticipate that which will be of significance, such as were its earlier studies on aspects of Soviet and Chinese biomedical practice and organizations.

During FY 1978, the following studies were in various stages of development:

Released for publication in FY 1978 —

- *Public Accountability and Peer Review in the United States and the United Kingdom* by S. Palmer and D.G. Gill of the University of Missouri at Columbia.
- *Policies for the Containment of Health Care Costs and Expenditures*, proceedings of an international conference, edited by S. Schweitzer, Georgetown University.
- *Changing National-Subnational Relations in Health: Opportunities and Constraints*, proceedings of an international conference, edited by C. Altenstetter, City University of New York.
- *Doctor-Patient Relationship in the Changing Health Scene*, proceedings of an international conference, edited by E. Gallagher, University of Kentucky.

In preparation —

- *An Introduction to American Medicine*, translation of an earlier publication into Russian, Spanish, and French, by J. Bowers, Josiah Macy, Jr., Foundation.
- *The British National Health Service: A Sociologist's Perspective* by D.G. Gill, University of Missouri at Columbia.
- *Universal Free Health Care in Canada, 1947-1977* by G. Hatcher, Albany Medical College of Union University.
- *Biomedical Research in Latin America and the Caribbean Area* edited by C. Kidd, George Washington University.

Fogarty Scholars-in-Residence Program

The Fogarty Scholars-in-Residence Program was established in 1968. Since then, 67 scholars from 18 countries have participated in the Program. Participation in the Scholars-in-Residence Program is by invitation. Scholars may be nominated from any discipline or field of work related to research in the health sciences. Final selection of candidates is made by the Director of the Fogarty International Center on the advice of the Scholars Advisory Panel. Citizens of any country can be appointed.

The Program objective is to conduct research studies on topics of contemporary importance in biomedical research. The role of the Scholars Program is to permit the inductive exploration of advanced research topics in an atmosphere removed from operational laboratory or administrative distractions. Scholars are chosen for the excellence of their scholarship, their professional standing, and their ability to interact with and stimulate others. Some Scholars who fill these criteria are invited to work on particular themes under study by the Fogarty International Center itself. Examples of themes are metastasis as a biological process, the origin and evolution of molecules, the influence of the genetic code on the evolutionary process, the role of nutrition in resistance to disease, and the relationship between human genetics and nutrition.

In FY 1978, 15 Scholars participated in the Program. Of these, eight were biochemists, which consistently claims the largest group of Scholars. Their activities ranged from close collaboration in experimental projects with intramural scientists to the organization of large conferences. The Program also furnished an opportunity for a number of talented scientists to complete writing for which they otherwise would not have had time or support. The freedom from teaching and administrative responsibility, coupled with easy access to the library facilities of the National Library of Medicine and in the Washington area generally, facilitated their task.

1. *Individual Activities and Publications.* The publications that appeared in FY 1978 are listed in the NIH Annual Bibliography. Publications generated by former Scholars are also included.

2. *Seminars and Lectures.* All the Scholars gave at least one lecture or seminar on a subject of their own choosing. They also took part in the ongoing seminars and journals clubs in different laboratories at NIH. The following is a partial list of formal lectures, cosponsored with the Foundation for Advanced Education in the Sciences:

December 1, 1977	Michael Schramm	"Coupling of Hormone Receptors to Adenylate Cyclase"
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December 15, 1977	H.Schachman	"Molecular Sociology of a Regulatory Enzyme"
January 23, 1978	Nathan Sharon	"Lectins, Their Chemistry and Interaction with Animal Cells"
January 25, 1978	M. Rocha e Silva	"Histamine, Anti-Histamine and Histamine Receptors"
February 16, 1978	G.N. Ramachandran	"A Physicist Looks at Biology"
February 24, 1978	Nathan Sharon	"Lectins in Host Parasite Relationship"
April 19, 1978	J. Waldenstrom	"Mono-Clonal Immunoglobulins with Defined Activity as Products of Random Repression"
April 24, 1978	Roger Stainer	"The Cyano-Bacteria Between Two Worlds"

Dr. Howard Schachman from the University of California came in September 1977 and spent two periods of 5 months broken by a visit of 2 months to several European laboratories. During his sojourn he organized several evening discussions on ligand binding and cell surfaces in collaboration with the other Scholars. He gave numerous seminars to different groups on the NIH campus as well as the public lecture listed above. Dr. Jan Waldenstrom worked extensively with NCI staff members on multiple myeloma. Together with Dr. Michael Potter of NCI, he convened a working group that examined the fundamental scientific knowledge about the disease and the clinical aspects of therapy. Primed by a Scholar and one or more collaborators on the campus, this type of informal workshop is particularly useful for the younger investigators as well as for NIH staff. Contact with versatile and erudite individuals who are at the top of their profession is always stimulating and leads to new insights and perceptions about one's own work.

Ten evening discussions on subjects related to structure and function of membranes were held in the Stone House. The Scholars as a group acted as a program committee for these meetings, but the principal impetus came from Drs. G. Salvatore and S. Ratner. They contacted the speakers, organized the program, invited the extramural participants from the Baltimore-Washington area and acted as hosts. The meetings were open to the scientific public. These discussions are being continued in FY 1979.

International Research Fellowship and Exchange Programs

The Fogarty International Center has always viewed as one of its most important functions for the advancement of biomedical knowledge the sponsorship of opportunities for U.S. scientists to work abroad, and foreign scientists to work in the United States for limited periods of time in direct collaborative projects. Such experiences broaden horizons, stimulate innovation, permit cost-effective sharing of resources, and upgrade scientific skills. Through cooperative arrangements with other countries and international organizations, the Center administers fellowship and exchange programs involving both U.S. and foreign scientists.

International Research Fellowship Program

The International Research Fellowship Program promotes collaborative biomedical research between U.S. and foreign scientists. The Program also offers a training opportunity for promising young foreign scientists in the formative stages of their careers. Collaboration provides the benefits of combined intensive research approaches, application of new and special skills, and the experiences gained from working with scientists in a unique environment and research settings outside the United States.

Fellows conduct collaborative research with senior biomedical research scientists in medical research institutions in any part of the United States as well as in the various intramural research components of the NIH. This Program, in addition to enhancing the health objectives of the U.S. Government, also enhances mutually profitable communication among scientists and assists in the health manpower development objectives of participating foreign countries.

In each participating country there is a national nominating committee, operating usually under the aegis of the appropriate central agency which conducts and supports biomedical research. The country committee screens all applicants from that country and nominates specified numbers of candidates to the Fogarty Center. These nominees compete with nominees from all other countries. Their proposals are reviewed by a scientific panel appointed by the Fogarty International Center to determine the scientific merit of the proposals. The applicants are ranked by the panel and awards are made on the basis of these rankings. In FY 1978, 86 new and 36 continuation awards were made with a total funding of \$2,038,000. Numerous publications have resulted from the work of the approximately 1,700 Fellows since the Program was established in 1958. Collaborative relationships usually continue thereafter. Many former Fellows now hold important and responsible positions in their home countries.

As examples of accomplishments, a recent Fellow characterized the reaction sequences of the biosynthesis of the antibiotic chlorothricin. By selective feeding of the microorganisms that naturally synthe-

size this antibiotic, he laid the groundwork for the test-tube synthesis and commercial production of chlorothricin. Another Fellow studied the immunology and physiology of oligodendrocytes. A knowledge of these supportive, nonneural brain cells is important for understanding the normal functioning of the brain and also certain diseased states such as Tay-Sachs disease. Research completed by other Fellows includes studies on cardiac microcirculation; immunology of cancer processes; toxic and carcinogenic metals in the human environment; dynamics of wound healing; hypertensive renal failure and body-fluid balance; immunological reactions of venereal herpes simplex virus; and neurochemical factors controlling respiration.

Senior International Fellowship Program

The Senior International Fellowship Program was initiated in 1975 to support highly qualified senior and mid-career faculty of U.S. schools of medicine, osteopathy, dentistry and public health for periods of study and research abroad. In FY 1978, eligibility for these fellowships was extended to equivalent faculty and staff of other biomedical research and educational departments and institutions. Fellowships are for 3 to 12 months and require nomination by the applicant's parent institution and invitation by a foreign host institution. The purpose of such fellowships encompasses not only the benefits of a period of productive scholarship abroad, but also enrichment of research and teaching careers and enhancement of scientific cooperation between U.S. and foreign institutions.

Interest and receptivity by U.S. scientists and their institutions and foreign host institutions in the Program has continued to grow since its initiation. Its productivity is being demonstrated in an increasing body of publications resulting from the work abroad. In the period FY 1975 through FY 1978, a total of 184 awards has been made to scientists from 67 institutions in 39 states. They have worked abroad in 25 countries, predominantly in Western Europe and the United Kingdom. Of this total, 64 awards were made in FY 1978 with funding of \$1,023,469.

Plans are being developed to include an allocation of additional Senior International Fellowships in certain special fields as a result of recommendations of several national commissions and interests of Institutes of NIH. Fields selected are aging, arthritis, diabetes, epilepsy, and tropical diseases. It is anticipated that about five fellowships in each field will be awarded in FY 1979. Recipients will be selected through a separate review and award cycle, with funding derived from the cooperating lead Institutes: NIA, NIAMDD, NINCDS, and NIAID. Further Program interests in the future will be to encourage a greater geographic dispersion of foreign host institutions and countries, particularly the less-developed or developing, where unique opportunities for research and mutual benefit can be expected.

International Neurosciences Fellowship Program

In cooperation with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the World Health Organization, the International Neurosciences Fellowship Program was established in 1977. It is designed to enhance the skills of health professionals and scientists of other countries in the neurosciences through training and experience in laboratories and institutions in the United States. Fellowships are awarded for periods of 6 to 12 months, and continuations beyond a year considered when adequately justified and if funds are available. The Program is administered by the Fogarty International Center with funds provided by NINCDS. Applications and initial screening are made from countries through WHO and its regional offices, with final selection by a committee at NIH on an individual, competitive merit basis. Initially, emphasis is placed on the convulsive disorders (epilepsy) and the cerebrovascular disorders (stroke). It is anticipated that six to eight fellowships can be awarded each year when the Program is fully operational. During FY 1978 the Program was being announced through WHO and several applications were being processed. The first awards are expected to be made early in FY 1979.

International Tropical Diseases Research Fellowship Program

The Fogarty International Center, in cooperation with the NIAID and with the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases, has established a program for a limited number of postdoctoral fellowships for advanced training designed particularly for candidates from countries in which specific diseases are indigenous. These diseases are malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, and leprosy. Administrative details have been developed among the cooperating institutions and announcements have been circulated to regional WHO offices and Ministries of Health. The first applications are expected during July 1979.

Other Research Fellowship Activities

The Swedish Medical Research Council and the Swiss National Science Foundation offer postdoctoral research fellowships for U.S. biomedical scientists who wish to pursue collaborative research in their countries. The Fogarty International Center provides application processing services and selection recommendations for these programs. The first awards by the Swedish program were made in 1963, and to date a total of 42 fellowships have been awarded. The Swiss program, begun in 1973, has awarded a total of 24 fellowships. Of these, three fellowships from the Swedish and five fellowships from the Swiss were awarded during FY 1978.

Individual Specialist Health Exchange Programs

Since 1975, the Fogarty International Center has administered the U.S.-U.S.S.R. Individual Specialist Health Exchange Program and the U.S.-Romania Health Exchange Program under intergovernmental agreements in science and technology. These programs provide mutual opportunities for health professionals to become personally familiar with various aspects of public health and biomedical research activities of the participating host country. By providing support for short- and long-term exchanges, the programs encourage and facilitate direct collaboration and communication between the health and biomedical communities of the United States and the Soviet Union and the United States and Romania. Through the promotion of person-to-person relationships, the basic goal of the exchange programs is to expand and disseminate scientific knowledge and to foster scientific growth.

In this endeavor, during FY 1978, the Fogarty International Center sponsored 11 individuals, one team of 2 persons, and one delegation of 5 persons, a total of 18 persons, for visits to the U.S.S.R. Two individuals and one delegation of three persons were sent to Romania. In the same period, 3 individuals, 4 teams, and 2 delegations, totaling 18 persons, were sent from the Soviet Union to the United States. No Romanian specialists participated in the exchange during FY 1978.

The following American specialists visited the Soviet Union during FY 1978:

Individuals

- Hugh Johnson, M.D., Rockford, Illinois, Plastic Surgery in the U.S.S.R.
- Elmer Ballantine, M.D., National Eye Institute, NIH: Retinal Dystrophy
- Albert Wertheimer, Ph.D., College of Pharmacy, University of Minnesota: Drug Delivery Systems and Pharmacy Services in Eastern Europe
- Lester Breslow, M.D., M.P.H., School of Public Health, UCLA: Health Measurement in the U.S.S.R.
- Leon Roizin, M.D., College of Physicians and Surgeons, Columbia University: Biological Psychiatry
- Samuel Corson, Ph.D., College of Medicine, Ohio State University: Psychiatry-Psychobiology
- Marshall F. Gilula, M.D., Life Energies Research Institute, Coconut Grove, Florida: Biofeedback Research
- David Hawkins, M.D., University of Virginia School of Medicine: Psychiatry Education in Eastern Europe
- Sait Tarhan, M.D., Mayo Clinic, Rochester, Minnesota: Cardiac Anesthesiology
- Joyce Kaufman, Ph.D., The Johns Hopkins University School of Medicine: Quantum Chemistry and Pharmacology

- John Petricciani, M.D., Bureau of Biologics, Food and Drug Administration: Virology

Teams

- Robert S. Hillman, M.D., Health Sciences Learning Resources Center, University of Washington, and Sheila Hillman, Seattle, Washington: Emergency Medical Care for Tourists in Russia

Delegations

- F.K. Mostofi, M.D., Armed Forces Institute of Pathology; Donald E. Henson, M.D., National Cancer Institute; Marjorie J. Williams, M.D., Veterans Administration; Robert Stowell, M.D., School of Medicine, University of California at Davis; and William Hartmann, M.D., Vanderbilt University School of Medicine: Pathology in the Soviet Union

The following American specialists visited Romania during FY 1978:

Individuals

- Albert I. Wertheimer, Ph.D., College of Pharmacy, University of Minnesota: Drug Delivery Systems and Pharmacy Services in Eastern Europe
- David Hawkins, M.D., University of Virginia School of Medicine: Psychiatry Education in Eastern Europe

Delegations

- J.E. Rall, Ph.D., National Institute of Arthritis, Metabolism, and Digestive Diseases; Hilton B. Levy, National Institute of Allergy and Infectious Diseases; and Ihor J. Masnyk, Ph.D., National Cancer Institute: U.S.-Romania Workshop on Biomedical Research Priorities

The following Soviet specialists visited the United States during FY 1978:

Individuals

- Dr. Mikhail Korolev, Institute of Poliomyelitis and Viral Encephalitis, Moscow: Virology
- Dr. Anatoli Erokhin, Second Moscow Medical Institute: Urology
- Dr. Alexandra Demidova, Central Institute of Postgraduate Medical Training, Moscow: Hematology

Teams

- Dr. Elena S. Ketiladza and Dr. Vera M. Stakhanova, Ivanov-sky Institute of Virology, Moscow: Hepatitis Research
- Dr. Lev I. Malyshv and Dr. Vladimir P. Sergiev, U.S.S.R. Ministry of Health, Moscow: Histoplasmosis
- Dr. Victor A. Knizhnikov and Dr. Boris K. Borisov, Institute of Biophysics, Moscow: Radiation Physics
- Dr. Nadezhda N. Bogomolova and Dr. Yuri S. Borishkin, Scientific Research Institute of Viral Preparations, Moscow: Rabies Research

Delegations

- Professor Tatiana V. Chervakova, Research Institute of Obstetrics and Gynecology, Moscow; Dr. Vera I. Lebedeva, U.S.S.R. Ministry of Health; Professor Vatsis M. Sadauskas, Kaunasskiy Medical Institute, Lithuania; and Dr. Yakov Solsky, Ukrainian Ministry of Health, Kiev: Obstetrics and Gynecology
- Dr. Gennadi M. Pakhomov and Dr. Oleg Glazov, Central Research Institute of Stomatoloty, Moscow and Dr. Kapiton Lakin, Moscow Medical Stomatological Institute: Dental Research.

The establishment of a scientist exchange program was agreed to during the year between NIH and the French National Center for Scientific Research (CNRS). The program would, in its initial phase, support each year up to five French scientists for research in the United States and a similar number of U.S. scientists in France. Implementation of the program is expected in FY 1979.

Coordination and Services for NIH International Relationships

The Fogarty International Center serves as the focal point for the coordination of international activities for the Director of NIH. The Center, as liaison point, has responsibility for facilitating communications between NIH and certain other international offices or agencies, including the HEW Office of International Health, the Department of State, U.S. embassies abroad, foreign embassies in Washington, D.C., and such intergovernmental organizations as the World Health Organization and the Pan American Health Organization. In addition, the Center provides certain central services necessary for effective overall NIH international affairs. These activities and services supporting the international interests of NIH as a whole for FY 1978 are summarized in the following sections.

Bilateral Agreements for Cooperation in Biomedical Research

Formal agreements for cooperation between governments of the United States and other countries provide the framework within which many international activities of NIH take place. While intensive biomedical cooperation may, and does, take place with many countries without the need for formal mechanisms, agreements form a basis for cooperation in particular situations and circumstances, such as to highlight priorities for concentration of mutual effort, to utilize special resources, or to overcome constraints of differing social and political systems.

Formal agreements between governments may also take a variety of forms, from those of broad scope for educational, cultural, and scientific exchange to more specific ones in science and technology or the health fields. In some instances health agreements may be subsidiary to a broader agreement in science and technology. Less formal technical-level agreements may also exist directly between counterpart institutes for a particular purpose.

NIH participation under agreements will usually be together with other agencies through channels of HEW. For several agreements, the National Science Foundation serves as the executive agency on behalf of the U.S. Government. General oversight for formal agreements rests with the Department of State.

The Fogarty International Center serves to coordinate NIH participation in formal agreements and provides operational liaison with other levels of HEW, the Department of State, the National Science Foundation, foreign embassies, and other appropriate organizations. Countries with which there are principal currently active agreements involving significant NIH participation include Egypt, France, India, Israel, Italy, Japan, Poland, Romania, Spain, Federal Republic of Germany, the Soviet Union, and Yugoslavia. NIH components have specific executive agency responsibilities with respect to the following formal agreements:

- Japan: U.S.-Japan Cooperative Medical Science Program (NIAID)
U.S.-Japan Cooperative Cancer Agreement (NCI)
U.S.-Japan Vision Research Agreement (NEI)
- Romania: U.S.-Romania Individual Health Scientist Exchange Program (FIC)
- U.S.S.R.: U.S.-U.S.S.R. Individual Health Scientist Exchange Program (FIC)
U.S.-U.S.S.R. Agreement for Cooperation in Artificial Heart Research (NHLBI)

Programs and activities during FY 1978 under these and other broader agreements are reported in detail in the sections of this report of each

responsible NIH component. Reference should also be made to the report of the Special Foreign Currency Program of the Fogarty International Center, which coordinates research projects under agreements for utilization of "P.L.-480" and related funds.

Special Foreign Currency Program

The objective of the NIH Special Foreign Currency Program (SFCP) is to extend NIH research activities into the international biomedical and health sciences community by supporting projects in certain countries where there are excess U.S. foreign currency credits and resources. These projects contribute to the domestic missions of the individual NIH operating units in the areas of biomedical research, translation, documentation, and dissemination of biomedical and health sciences information. Collaborative research agreements for these individual research projects involve U.S. biomedical scientists from within NIH intramural laboratories as well as in U.S. academic and foreign research institutions, thus assuring that academic, intellectual, and scientific benefits accrue to the United States as well as to the participating foreign country, institutions, and scientists. The program is an integral and significant part of the NIH international and domestic effort to advance biomedical science knowledge.

The Special Foreign Currency Program is supported with a unique source of funds referred to as "excess currencies." These funds have accrued to the credit of the U.S. Government primarily from the sale of agricultural products for payments in local foreign (nonconvertible) currency under Public Law 480, The Agricultural Trade Development and Assistance Act of 1954. It is from this source that the term P.L.-480 program is derived and is a misnomer when applied to this NIH program. After 1967 such sales had to be made for dollars with the result that the U.S. foreign currency balances are not being replenished as they are used. Excess currencies are those U.S.-owned foreign currencies in a country which are determined by the Office of Management and Budget (OMB) to be excess to the needs of the U.S. Government during the next 2-year period. Countries where such currencies are available are referred to as excess currency countries. When the balance of a currency drops below this level, but is of a sufficient amount to be made available for special purposes or in limited amounts with restriction, the currency is designated by OMB as a near excess currency. A list of countries where currencies are excess or near excess is issued by OMB at the beginning of each fiscal year. The near excess currency countries at present are: Morocco, Poland, Tunisia, and Yugoslavia. These currencies will continue to decrease in amount and are not available for the NIH Special Foreign Currency Program. The excess currency countries are: Burma, Egypt, Guinea, India, and Pakistan.

Funds for the NIH Special Foreign Currency Program are included with those of other Public Health Service agencies in the HEW appropriation for Scientific Activities Overseas, reviewed and acted upon annually by the Congress of the United States. Although the appropriation is expressed in terms of dollars, it is actually an authorization to use only excess foreign currencies up to the dollar equivalent of the amount appropriated. This Program does not result in a flow of dollars abroad or place an annual requirement upon new tax revenues.

The appropriation is made to the Office of the Assistant Secretary for Health (ASH), HEW. The Office of International Health has responsibility for formulating policies of the SFCP and apportioning the appropriation. Funds are allotted to NIH on the basis of conformance of a project to programs and priorities of HEW and priorities of foreign countries that have been negotiated by HEW. When funds are limited for some reason, NIH projects must compete with those of other health agencies. NIH has responsibility only for reviewing its projects for technical merit and contribution to NIH programs. This may occasionally result in the anomalous situation wherein a project is found meritorious upon review by NIH consultants but is not selected for funding.

With the maturation of this and similar programs of other HEW and U.S. agencies, the use of these funds has been extended through the years from 3 agencies (originally HEW, the Department of Agriculture, and the Department of State) to presently 13 science and technology agencies. The increased demands upon the funds have depleted balances in some cases to where they are marginal, such as in Poland, and to where they are no longer available, as in Israel, Tunisia, and Yugoslavia. In response to a need for coordination of such increased U.S. activity abroad, and to assure effective management and utilization of remaining funds, the Department of State has entered into bilateral agreements with governments of the excess or near excess currency countries for cooperation in science and technology, including the health sciences. In some cases joint funds, to which each country contributes equally, have been established under these agreements to alleviate the impact of the loss of total U.S. support and to provide a phase-out period for terminating projects with maximum data recovery or for seeking support from other sources. In India and Yugoslavia biomedical and health sciences are provided for under the Science and Technology Board; in Poland and Egypt there are separate Biomedical and Health Science Boards. Department of State and Office of the Assistant Secretary for Health, HEW, representatives serve on these boards, which set the general program parameters and priorities to which NIH programs must conform. The success and productivity of such agreements, however, remain dependent upon scientist-to-scientist collaboration on problems of mutual interest, critically selected for their potential of furthering the understanding of normal life processes and disease states of man. This characterizes the NIH program and is equally important to the improvement of health in the countries where the SFCP is active.

Since the 1962 inception of the NIH-SFCP, 212 U.S. scientists, 243 foreign scientists, 93 U.S. academic institutions, 110 foreign institutions, and 11 NIH Institutes have participated in the program. These figures do not include the many foreign professional staff serving in supporting but essential roles in the projects.

More than half of the responsible foreign Principal Investigators on the research projects supported under this program have had U.S. training. By means of this program, the U.S.-trained foreign scientists have been able to maintain an active collaboration with their U.S. preceptors and thus remain a part of the U.S. biomedical science community. In some instances, by virtue of the research support, these young biomedical scientists have been able to introduce modern concepts of medical training, clinical investigation, biomedical research, and patient care that will have long-term effects within the country. The immediate contribution to biomedical research from these countries is thus only one of the benefits from this program.

Through the SFCP, NIH has engaged the unusual talents of some of the most outstanding scientists throughout the world and utilized unusual research opportunities for health-related projects of importance to the American people. A number of significant advances in biomedical research have been reported and documented in over 3,000 publications in the scientific literature as the result of U.S. and foreign investigators pooling their talents and resources to search for information which will help in the understanding, prevention, and treatment of diseases.

It is not the intention or objective of NIH to provide technical assistance or foreign aid under this program. These are activities outside the statutory mission of NIH. However, it must be recognized that research projects, if they are to be conducted in a country, must represent the mutual interest of the host country, its institutions, and medical personnel, and that therefore financial, academic, intellectual, and scientific benefits do accrue to the host country. Although this has not been a primary consideration of NIH, the HEW and the State Department have recognized that this program has made significant ancillary contributions to humanitarian, technical assistance, U.S. policy, and political objectives of the United States. The biomedical and health science base established by the NIH-SFCP in past years has served as the basis for formal bilateral agreements expanding collaboration of other U.S. agencies into the areas of science and technology in Egypt, India, Israel, Poland, and Yugoslavia.

Egypt

The Special Foreign Currency Program in Egypt is characterized by the participatory role of the Fogarty International Center in the activities of the Subcommittee for Biomedical Research of the U.S.-Egypt Joint Working Group on Health Cooperation established by an

agreement of October 28, 1975. The Director of the Fogarty International Center is the U.S. Cochairman and the SFCP Branch serves as the Secretariat for the Subcommittee. Four major events marked the activities of the SFCP during this year. They were: (1) the first meeting of the full Subcommittee for Biomedical Research held in Cairo, January 1978; (2) the U.S.-Egypt Joint Working Group on Health Cooperation meeting in Egypt in June 1978; (3) the survey of Liver Disease and Hepatitis; and (4) the projected limitation on funds for future years.

The U.S. component of the Subcommittee for Biomedical Research selected several U.S. researchers working in areas identified during previous meetings of the Joint Working Group on Health Cooperation and Subcommittee for Biomedical Research as of importance to Egypt, i.e., (1) tropical diseases; (2) infectious diseases and immunology; (3) rabies, (4) diabetes; (5) enteric and diarrheal (viral and bacterial) diseases; (6) nutrition; and (7) child health, and arranged for their participation in a survey of these topics during its January 1978 meeting in Egypt. Although liver disease and hepatitis were also identified at that time as of importance, consideration was deferred for a subsequent visit of a survey team of researchers on these subjects. During the visit, working groups composed of U.S. and Egyptian researchers in the foregoing priority areas were organized and their deliberations and recommendations were recorded in individual reports which were incorporated into the report of the subcommittee. The conclusions of these working groups and the subcommittee were reviewed with the Minister of Health. This report will serve as the Biomedical Research Subcommittee's plan for developing its research program and integrating its activities with those of other subcommittees.

The subcommittee recommendation with the broadest implication for research program development and potential impact on health in Egypt was the proposal for the establishment of a center for collection of incidence, prevalence, morbidity, and mortality data, as a basis for objectively determining the disease and health problem priorities of Egypt and evaluation of intervention programs. These centers will also serve as sites for the conduct of research, such as a comprehensive study of infant enteric and diarrheal diseases identified by the subcommittee as its second priority.

India

The NIH collaboration with Indian scientists under the Special Foreign Currency Program began with the signing of the first research agreement in 1961 for a study of protein malnutrition. Despite the research potential of India and the close professional and academic ties between U.S. and Indian scientists, the program remained at a modest level of activity until it was interrupted in July 1972 by the Indian

Government's decision to undertake a review of all U.S.-rupee supported programs and to establish new project review and selection procedures. The SFCP was essentially phased out over a 5-year period subsequent to that date.

The program has always been well received by individual scientists within India and among their U.S. counterparts. However, the lack of uniform Government policy in India concerning the SFCP, the large number of autonomous Government agencies and semiautonomous institutions representing both diverse and complementary interests, and the absence of a coordinating point with uniform procedures have been a deterrent to expansion of the program to a size commensurate with Indian research potential. At one time, the NIH-SFCP included projects which originated from and were the responsibility of six different Indian Government agencies.

This situation was changed significantly by the Agreement between the Government of the United States of America and the Government of the Republic of India to Establish a Joint Commission on Economic, Commercial, Scientific, Technological, Educational, and Cultural Cooperation which was signed on October 28, 1974, by Secretary of State Kissinger and Mr. Y.B. Chavan, Minister for External Affairs of the Republic of India. The agreement provided for establishing subcommittees for the fields of economic and commercial development, scientific and technological cooperation, and educational and cultural cooperation. The Subcommittee on Science and Technology was given responsibility for health as well as industry and agriculture. The first meeting of the U.S.-Indo Subcommittee on Science and Technology was held in January 1975 in Washington, D.C. Subsequent meetings were held in January 1976 in New Delhi and in June 1977 in Washington.

At the first meeting of the Subcommittee on Health, the Ministry of Health, and Indian Council of Medical Research (ICMR) took the initiative, setting priorities for collaboration which they have kept sharply in focus during subsequent meetings and in guiding program development. The priorities agreed upon at the initial meeting, and which remain in effect are: (1) communicable and infectious diseases, with particular emphasis on prevention and control techniques for such diseases as tuberculosis, leprosy, malaria, filariasis; (2) reproductive biology and fertility control; (3) health delivery systems for efficient utilization of medical and paramedical manpower; (4) nutritional, metabolic, and degenerative diseases; (5) toxicologic research on naturally occurring toxins in foods, pesticides, and drug residues; and (6) other such areas of biomedical and health science research as may be proposed and agreed upon as being of mutual interest and importance.

During this year, definitive action was taken on 15 projects of interest to NIH for which an Indian decision had been pending for an extended interval during the review period. Although none was selected for support by the NIH-SFCP, several of those found meritorious but for which collaboration was not essential to conduct of the study, were supported with Department of Science and Technology or ICMR funds.

The collaboration was reestablished under the newly created Sub-commission with initiation of two projects which were activated this year: one, a study of urolithiasis, especially of the bladder, a significant problem in India; and the other a more fundamental investigation of the physical-chemical basis for the therapeutic properties of lithium, and of the pathology of reactions of free radicals in biological systems. The renewal of an unusually productive study of oral cancer and associated oral pathology, which was interrupted for 3 years during the review period, was also activated.

The SFCP has worked closely with the ICMR and NIH Institutes in directing U.S. attention to such high priority problems in India as leprosy. In the previous year a team of four U.S. scientists attended an initial session in India of a two-part Leprosy Research Planning Conference (March 1976) at the invitation of the ICMR and under the auspices of the SFCP. The conference was designed to introduce the U.S. participants to Indian leprosy problems, clinical and research facilities, and clinical investigators and biomedical scientists. The survey panel visited 12 institutions in India. In this year (October 1977) the second part of the Leprosy Planning Conference was held, in which 10 Americans participated. This second session was dedicated to identifying potential lines of investigation, arranging scientist-to-scientist collaborations and preparing synoptic research protocols to be developed subsequently into detailed project descriptions for submission to the ICMR and forwarding to NIH. Among the aspects of leprosy given attention at this meeting were immunology, immunogenetics, microbiology, pathology, cultivation, animal models, nutrition, vaccines, chemotherapy, biochemical pharmacology of antileprosy drugs, and drug development. These activities have been productive of research proposals accepted by the ICMR and presented for consideration by NIH.

The NIH collaborates informally with the Madras Medical College and Tuberculosis Chemotherapy Center in a study of the immunological and clinical aspects of human filariasis, with particular attention to tropical eosinophilia an active and productive area of special interest to the ICMR. Malaria and reproductive physiology areas, which NIH has surveyed in cooperation with the ICMR, remain of mutual interest and offer potential for future cooperation.

Israel

In FY 1968, the balance of U.S.-owned Israeli pounds was depleted to the point where it was determined that funds would no longer be available for the SFCP. This was disruptive to biomedical and health sciences in Israel, where 50 percent of the research effort in these fields was dependent upon U.S. support. In anticipation of the loss of these funds and to provide some alternative support, the Department of State and the Israeli Government signed an agreement on September

27, 1973, establishing the U.S.-Israeli Binational Science Foundation, to which each country contributed equal amounts of Israeli pounds in a total equivalent to \$60 million. The income from the investment of these funds provides for a modest number of new projects annually. This was the first of several joint funds to be established subsequently under similar circumstances in other countries.

Applications for support from the Foundation are submitted to the Executive Director of the U.S.-Israel Binational Foundation, P.O.B. 7677, Jerusalem. The Foundation reviews and evaluates the technical merit of applications. The opinions of U.S. scientists are solicited in the review process. The Board of Governors of the Foundation, on which U.S. Government representatives and private citizens, as well as Israeli members serve, makes recommendations on projects to be funded. By the terms of the agreement, the Foundation projects must contribute to the biomedical science programs in the United States as well as Israel. In keeping with this requirement, NIH is requested annually to review the newly submitted applications for their relevance to NIH biomedical research programs. This function is carried out by the NIH-SFCP. The Foundation also sends to NIH annual progress reports from all biomedical science projects. These are also received, and if necessary distributed, by the SFCP. Information about the Foundation, its Annual Report, and application forms are maintained by the SFCP Branch and distributed upon request. The Foundation's most recent (1977) report lists 118 active projects in the categories of Life Sciences and Health. 12 of which are collaborations with NIH intramural staff.

Pakistan

There is no Science and Technology or Health Agreement with Pakistan. The modest size of the NIH Special Foreign Currency Program and the delays to which projects are subject in the review process may be attributed to the lack of recognition given to the biomedical and health sciences, in contrast to that which a formal bilateral agreement accords them in other countries. The Pakistan Medical Research Council and Pakistan Science and Technology Council always have been receptive to collaborative research proposals. The Ministry for Finance and Economic Planning, however, requires that research projects be an integral part of the Five Year Plan. Predictably, intellectual spontaneity does not coincide with economic planning cycles, with the result that discouraging delays occur in the process of obtaining authorization for use of funds to support individual research projects. The recent focus of the program has been upon the chemistry of products of potential pharmacological importance from indigenous plants. The Council for Scientific and Industrial Research has been active in this area and a number of proposals from this organization have been submitted to NIH.

A Memorandum of Understanding between the United States and Poland, signed on March 14, 1962, designated NIH as the focus for development of a collaborative research program in the biomedical sciences. The first NIH research collaboration in Poland was a study of neuromuscular diseases in the Department of Neurology of the Medical Academy of Warsaw, which is still active but in a much different form.

With expansion of the program and changes in its emphasis, as well as reorganizations of HEW, responsibility for the program was ultimately transferred to the Office of International Health, Office of the Assistant Secretary for Health, and the original bilateral agreement which served as the basis for the collaboration was revised to bring it up to date and to expand its scope.

On March 15, 1973, during the visit of the Minister of Health of Poland, a revised Memorandum of Understanding was signed by the Secretary of HEW and Dr. Marian Sliwinski, the Polish Minister of Health. This agreement, for the first time, formally provided for: (1) the exchange of scientists; (2) the development of mutually agreed-upon priorities; and (3) the annual review and revision of these priorities.

On October 8, 1974, during the visit of Mr. Edward Gierek, First Secretary of the Polish United Workers Party, the health agreement of 1973 was revised and elevated to the status of a country-to-country agreement. This agreement included two new provisions: (1) establishment of a U.S.-Polish Joint Committee for Health Cooperation; and (2) funding of HEW projects from the Marie Skłodowska-Curie Fund. This Joint Fund was established by the separate agreement for Funding of Cooperation in Science and Technology, which was also signed at that time (October 8, 1974). This document, which also provided for the establishment of a U.S.-Polish Joint Board (for science and technology), was an implementation of the Science and Technology Cooperation Agreement, signed in October 1972 during the visit of the President of the United States to Poland.

About the time that the Joint Fund was created, the Office of Management and Budget placed a limitation on use of funds, and the Treasury Department and the Department of State issued a schedule for phasing out full or total support of projects with U.S.-owned zlotys by December 31, 1976, at which time Poland was removed from the excess currency list.

With the establishment of the Joint Board and the Joint Fund, and the announcement of the U.S. funding phase-out schedule, the Polish Government agreed to make contributions to the Joint Fund in amounts equal to those which HEW and other agencies deposited each year during the 4-year phase-out period to December 31, 1976, for support of NIH and other agency research projects. The Polish contributions to the Joint Fund were to become available January 1, 1977. Unfortunately, the time and difficulty of working out fiscal and administrative procedures for the comingling and disbursement of U.S. and

Polish contributions to the Joint Fund, subject to fiscal constraints of the two Governments, was greater than anticipated. These procedures were finally agreed upon at a meeting of the U.S.-Polish Joint Board for Science and Technology, April 1978, in Washington.

The current program priorities were established at the first meeting of the U.S.-Polish Joint Committee for Health Cooperation and reviewed at the second meeting with the result that oncology, which had been deleted at the time of the first annual review, was reinstated. The last formal meeting of the Committee was in March 1976 and the priorities, which have been reported previously, were not reviewed at that time. The Committee coordinators, however, have met annually since that date to transact business when necessary.

The hiatus of support in excess of 2 years and resulting uncertainty as to when and under what conditions funds would be available disrupted the SFCP continuity and discouraged many U.S. scientists interested in collaborating with associates in Poland. The agreement upon Joint Fund procedures permitted NIH to immediately renew support of projects which had been interrupted during this period and to activate the first new project to be supported under these procedures. Each project supported by the Joint Fund has travel funds for visits of collaborating scientists. However, the Joint Fund has no travel funds available for planning purposes. This is a major deterrent to establishing collaborations between scientists who need to meet for the purpose of learning about the environment in which the project will be conducted, assessing joint resources, and developing the experimental design of the study in sufficient detail that it can successfully withstand the scrutiny of the NIH review process. With evidence that the Joint Fund is operational, the SFCP has begun to resume a normal level of operation. This perception was further reinforced by the subsequent visit of the Director of the Fogarty International Center to the Coordinating Commission for the Polish-American Scientific Collaborations, the Scientific Council to the Ministry of Health and Social Welfare, and to several NIH research projects and other research centers in Poland.

Yugoslavia

The NIH-Yugoslav research collaboration under the Special Foreign Currency Program was initiated in 1962. In March 1972 it was found unexpectedly that the balance of U.S.-owned dinars was depleted to the point that they were no longer available for this program of NIH and other agencies. The Department of State negotiated the Agreement between the Government of the United States of America and the Government of the Socialist Federal Republic of Yugoslavia on Scientific and Technological Cooperation, which was signed on May 18, 1973.

This agreement established a Joint Fund for the support of scientific and technological projects, including health, and a U.S.-Yugoslav

Joint Board on Scientific and Technological Cooperation to administer the Fund in the amount of \$14.4 million (equivalent) from equal dinar contributions by each country. At a meeting of the Joint Board, May 14-18, 1973, it was apparent that the income from this Fund would have little effect in moderating the loss of financial support; the decision was then made to commit all the funds to provide limited support for projects during a phase-out period. NIH was allotted funds for 24 projects. Of these, eight remain active as a result of reducing expenditure rates to extend the financial basis for collaboration.

The U.S.-Yugoslav Joint Board on Scientific and Technological Cooperation meets twice a year, a Fall meeting in Yugoslavia and a Spring meeting in the United States. The U.S. members of the Board are the Science Attache from the American Embassy in Yugoslavia and a representative from the staff of the Bureau of Oceans and International Environmental and Scientific Affairs, U.S. Department of State.

The Joint Board at its October 1977 meeting in Yugoslavia apportioned a small amount of dinars from both uncommitted funds carried forward from unused initial deposits and from interest accumulated on deposits among several projects of various U.S. agencies. Two NIH projects were the beneficiary of these funds.

With diminishing funds the Joint Board has been occupied with efforts to maintain collaboration between scientific communities of the two countries and finding a basis for transition to the other sources of support. To this end, a list of proposed research topics in various fields of science and technology was presented at this meeting for review by U.S. agencies. In a followup of this effort, synoptic proposals outlining these topics in greater detail were presented at the May 1978 meeting of the Joint Board in Washington for more extensive consideration by interested agencies. Forty-one of these were referred to NIH.

The U.S.-Yugoslav bilateral agreement has a unique provision for matching U.S. dollar support of any former NIH-SFCP, Joint Board or new research project of mutual interest on an equal-share matching basis through the Joint Fund administered by the U.S.-Yugoslavia Joint Board on Scientific and Technological Cooperation. Scientists in Yugoslavia are also eligible and encouraged to apply directly to NIH for support from the regular (dollar) research grant programs.

International Visitors Center

The NIH attracts many scientists, administrators, and health professionals from all parts of the world to visit, examine and exchange ideas and techniques in the biomedical sciences. The International Visitors Center (IVC) has been established by the Fogarty International Center to provide the administrative management of the NIH Visiting Program for the Institutes and Divisions of NIH, and to provide a full range of advisory and facilitative services to foreign scientists in the

Guest Scientist Program and the Expert Programs of the BID's. In addition, the IVC serves as a focal point for short-term foreign visitors to assist in the reception and programming of their visits to NIH.

In addition to the NIH Visiting Program participants, the International Visitors Center provided a full range of advisory and facilitative services to some 350 other foreign scientists who came to NIH during FY 1978 to participate in NIH research studies. Among this number were 232 scientists from 37 foreign countries, primarily the affluent developed ones, who came as Guest Scientists funded by their countries, international agencies, or U.S. sources other than NIH. An increase in the number of Guest Scientists from the developed nations has been observed, and it is anticipated that this trend will continue in the future.

The additional 120 scientists, whom we have served, include experts appointed by the Institutes, and scientists coming to NIH under sponsorship of the bilateral agreements in which NIH participates. Similar increases in the numbers of experts and exchange scientists are expected in the future, due to the expansion of the programs represented by this group.

The International Visitors Center also serves as a focal point for foreign scientists, administrators, health professionals, and dignitaries from all parts of the world who want to visit NIH during the course of their travels. The IVC is responsible for arranging appointments, briefings, demonstrations, and tours of the biomedical facilities in accordance with the special interests of these international visitors. During FY 1978, extensive programs were arranged for 78 visitors from 27 countries, and there were numerous other visitors for more limited activities.

The NIH Visiting Program

This program offers distinguished and talented scientists at all levels of their careers the opportunity to come to NIH to share the tremendous resources of the NIH for an interchange of scientific information and training. This program enhances the environment of NIH by facilitation of the advancement of knowledge in the health sciences, and exerting a significant influence on the development of biomedical research internationally by implementing close and continuing working relationships between Visiting Program participants and the research staff of NIH.

The NIH Visiting Program is composed of: *Visiting Fellows*, authorized by Sections 207(g) and 307 of the Public Health Service Act and 42 CFR, Part 61A of the PHS Regulations for regular fellowship awards; and *Visiting Associates and Visiting Scientists*, authorized by Sections 207(g) and (h) of the PHS Act, and Part 61B of the PHS Regulations for service fellowship appointments.

The NIH Visiting Program, which was initiated in August 1950, has continued to grow at an accelerating rate. In FY 1965, there were

157 participants at a cost of \$1.2 million; in FY 1971, 225 at \$2.6 million; and in FY 1976, 624 at \$6.8 million. The following table contrasts the participation in the last 2 years:

NIH VISITING PROGRAM

Foreign Country	FY 77		FY 78	
	Number of Participants	US \$	Number of Participants	US \$
Argentina	7	82,301	8	73,639
Australia	14	127,922	24	210,527
Austria	5	49,693	8	57,444
Belgium	17	172,280	15	168,576
Bolivia	1	4,452	--	---
Brazil	7	38,330	5	63,051
Bulgaria	1	6,214	--	---
Cameroon	2	25,298	1	16,849
Canada	17	171,492	24	218,929
Chile	3	24,873	2	28,634
China-Taiwan	38	389,062	12	156,415
Czechoslovakia	1	19,169	2	10,125
Denmark	4	29,695	1	6,087
Egypt	4	43,307	4	59,104
Finland	2	18,153	5	63,696
France	10	68,947	19	141,193
Germany	12	116,185	15	158,517
Greece	6	64,325	7	118,228
Guatemala	1	10,849	1	10,763
Hong Kong	1	1,758	4	17,540
Hungary	4	34,619	3	15,939
Iceland	--	---	1	9,151
India	61	582,876	67	642,713
Iran	1	3,734	--	---
Ireland	2	28,543	2	36,863
Israel	44	614,579	44	535,598
Italy	48	505,228	53	562,730
Japan	156	1,643,427	175	1,944,871
Korea	1	3,667	6	22,903
Lebanon	--	---	3	21,551
Luxembourg	--	---	1	3,029
Malaysia	2	15,397	2	22,259
Mexico	5	43,072	3	49,173
Nepal	--	---	1	1,320
Netherlands	5	54,800	7	36,465
New Zealand	5	44,737	1	6,133
Nigeria	1	13,821	2	38,349
Norway	3	38,381	2	4,218
Pakistan	2	18,889	3	48,048
Peru	2	34,689	2	30,805

Foreign Country	FY 77		FY 78	
	Number of Participants	US \$	Number of Participants	US \$
Philippines	2	34,250	1	2,920
Poland	14	152,927	9	76,766
Portugal	1	9,236	1	11,840
South Africa	5	59,850	2	70,557
Spain	9	97,954	12	113,285
Sri Lanka	2	18,115	3	26,281
Sudan	--	---	1	1,746
Sweden	7	73,228	14	176,121
Switzerland	13	168,789	14	198,090
Thailand	--	---	1	3,157
Turkey	2	17,285	3	22,751
United Kingdom	65	668,594	73	894,997
Venezuela	1	10,839	--	---
West Indies	1	11,690	--	---
Yugoslavia	2	23,703	--	---
<hr/>				
Total participants:				
Foreign countries	617	6,266,639	675	7,269,174
United States*	178	2,763,559	187	2,925,379
<hr/>				
Grand Total	795	\$9,030,198	862	\$10,194,553
<hr/>				
Total countries:	60		57	
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* U.S. includes citizens, permanent residents and conditional immigrants.

During FY 1978, in the NIH Visiting Program, there were 513 Visiting Fellows, 184 Visiting Associates, and 165 Visiting Scientists. During the same year, there were 276 new appointments and 265 terminations, providing the turnover so vital to the exchange nature of the program. A significant number of former participants in the program returned to NIH in subsequent years, bringing their advanced knowledge and new insights to revitalize their working relationships with NIH staff scientists. Some of the international collaborative programs had their inception in the NIH Visiting Program. In addition, some Fogarty Scholars were former participants in the Visiting Program. Among the latter are former Visiting Scientists Torsten Teorell of Sweden; Osamu Hayaishi of Japan; Michael Sela of Israel; Ruggero Cepellini and Gaetano Salvatore of Italy.

Four former Visiting Scientists in the Visiting Program were awarded the Nobel Prize in Physiology or Medicine:

- 1947 — Dr. Bernardo A. Houssay of Argentina, for the discovery of the role of pituitary hormone in sugar metabolism.
- 1962 — Sir Francis H.C. Crick of the United Kingdom, for the discovery of the molecular structure of nucleic acids and its significance in the transmission of genetic information.
- 1968 — Dr. H. Gobind Khorana of the United States, for translation of the genetic code and its function in protein synthesis. Dr. Khorana shared this award with Dr. Robert W. Holley and Dr. Marshall W. Nirenberg, the latter, an NIH scientist.
- 1976 — Dr. D. Carleton Gajdusek of the United States, for work on atypical slow viruses.

During the many years of his work leading to the Nobel Prize, Dr. Gajdusek collaborated with two Australian scientists, who periodically returned to his NIH laboratory under Visiting Program sponsorship. Dr. Vincent Zigas has come as a Visiting Scientist on a number of occasions since 1958 to work with Dr. Gajdusek and bring to the studies the benefits of his field observations on Kuru in New Guinea. Dr. Michael Alpers, also of Australia, has also come to NIH, both as a Visiting Associate and a Visiting Scientist, to work with Dr. Gajdusek in this study. This is a fine example of the benefit of this program which enables a continuing exchange of scientists and the encouragement of long-term collaborative studies in the geographical locations where such research can prosper most effectively.

It is anticipated that the growth pattern of the NIH Visiting Program will continue to follow the experience of recent years.

International Education Program

The International Education Program, originally established in 1945, was under other Public Health Service agencies before being assigned to the Fogarty International Center. The Program has two principal functions:

1. The location and arrangement of short-time training placements for foreign health professionals coming to the United States under the sponsorship of the World Health Organization, the Agency for International Development, private foundations, or as voluntary visitors. Training programs vary from technical training for individuals from underdeveloped countries to programs for highly specialized personnel from advanced countries.
2. The solicitation and receipt of applications from American health professionals for WHO fellowships to study

advanced aspects of health care throughout the world. Geriatrics, neonatal care, and Government-financed health systems are the most popular fields of study for Americans.

During FY 1978, 244 training requests were from WHO, 67 from the Agency for International Development, and 9 from voluntary visitors through the Department of State. The Center's WHO fellowship selection committee reviewed 63 applications, recommending that 20 of these be awarded a WHO fellowship.

During FY 1978, these training programs varied in length from 1 week to 1 year, with an overall average of 3 months.

U.S. Government Support of The Gorgas Memorial Laboratory, Panama

On May 7, 1928, President Coolidge signed Public Law 30-750 whereby Congress authorized a permanent annual appropriation to the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., Washington, D.C., for the operation and maintenance of a research laboratory in Panama. This action, together with land and building donated by the Government of Panama, permitted establishment of the Gorgas Memorial Laboratory. This year, 1978, thus marks the 50th anniversary of its founding. Since FY 1971, the Fogarty International Center budget has provided the annual U.S. core support funds. The Center maintains general program oversight.

The Laboratory conducts a diversified program of research in tropical disease of importance to the United States, Panama, and the region. Particular emphasis is placed upon virology, parasitology, and the effects of environmental change on disease vectors and transmission. In addition to research, the Laboratory makes its facilities available for visiting scientists and the training of professional personnel. It has cooperative arrangements with several U.S. universities for graduate and medical student study and course credit. Formal training courses in tropical medicine are conducted several times a year for U.S. Navy medical officers.

The work of the Laboratory is summarized in annual reports to the Congress and in publications in the scientific literature by its staff. Highlights during FY 1978 included:

- demonstration that Gamboa virus is transmitted transovarially in the *Aedes squamipennis* mosquito. This is the first demonstration of transovarial transmission of a neotropical virus and raises the question of the importance of this mechanism in maintaining arbovirus between outbreaks of disease.

- an advance in the ability to classify insects was made possible through the isozyme technique, which permits rapid speciation of insects that previously could be differentiated only with difficulty.
- continuation of antimalarial drug evaluation using the *Aotus* monkey gave promise of effective compounds for the future. Seroepidemiologic methods indicate the feasibility of rapidly determining the malarial status of an area.
- support to the national authorities of Honduras, Guatemala, and El Salvador in the investigation of an outbreak of dengue, the first reappearance of the disease in over 30 years. The rapid spread of dengue is of great concern since it indicates the prevalence of *Aedes aegypti*, which could reintroduce yellow fever into these countries.
- expansion of the Laboratory's range of research interest occurred with the detection of an area of Panama with an apparent high prevalence of cancer of the cervix. A study was initiated with a view to defining its epidemiology, cause, and ultimate prevention. U.S. Government core support of \$1.4 million was provided in FY 1978.

In addition, the Laboratory derived \$484,454 from research grants and contracts from other sources.

International Cooperation by Components of NIH

National Cancer Institute

Introduction

Striking differences in geographic, environmental, occupational, and social conditions of peoples throughout the world suggest that these variations must have a critical influence on the incidence and the types of cancer prevalent in a given area. Through collaboration with international organizations and scientists from foreign institutions, the National Cancer Institute (NCI) is becoming increasingly aware of the crucial factors for improving the quantity and quality of health services required for coping with the cancer problem. By participation in international cancer research activities, the NCI can ensure more rapid advances in basic research and its application to the clinical management and control of cancer.

Accordingly, the contribution of NCI to the international struggle against cancer includes (1) continuing support of research on cancer by foreign scientists who are highly qualified and have unique expertise; (2) support of cooperative research programs, principally under bilateral agreements with foreign governments, institutions, or organizations; (3) maintenance of liaison and research collaboration with international organizations and agencies that have well-defined objectives in cancer research and cancer treatment/prevention; (4) support of training foreign scientists in the United States as well as the interaction of American scientists with colleagues in foreign laboratories; and (5) management and operation of an International Cancer Research Data Bank for promoting and facilitating, on a worldwide basis, the exchange of information for cancer research and treatment.

The International Cancer Research Data Bank Program

The International Cancer Research Data Bank (ICRDB) Program is one of the National Cancer Institute's principal modes for worldwide communication of scientific information. Its objective is to promote and facilitate the exchange of information between cancer scientists and to disseminate information to physicians through cancer centers and other appropriate organizations for the ultimate benefit of the cancer patient. Mandated by the National Cancer Act of 1971, this mission of the ICRDB program is accomplished by (1) the operation of *several on-line*

computer data bases; (2) the publication of a number of *technical bulletins;* and, (3) the support of a variety of *specialized information collection, analysis, and dissemination activities.*

The major feature of the ICRDB program is a computer-based information system called CANCERLINE (Cancer Information On-Line). CANCERLINE links the computer system at the National Library of Medicine in Bethesda with terminals in more than 700 locations throughout the United States and 11 foreign countries: Australia, Brazil, Canada, France, West Germany, Iran, Japan, Mexico, South Africa, Sweden, and the United Kingdom.

CANCERLINE contains three data bases. One, CANCERLIT (CANcer LITerature), contains more than 150,000 abstracts of the world's published literature in all fields of cancer. Another data base, CANCERPROJ (CANCER PROJects), contains more than 20,000 descriptions of cancer projects currently in progress. Included are more than 4,000 descriptions from foreign investigators located in some 60 different countries. The project descriptions are selected and processed by the Current Cancer Research Projects Analysis Center (CCRESPAC), which is operated for the ICRDB program by the Smithsonian Science Information Exchange. CCRESPAC also compiles these project descriptions into SPECIAL LISTINGS, which deal with some 60 specific research topics. The third data base, CLINPROT (CLINical Cancer PROTOcols), contains about 1,000 summaries of clinical evaluations of new therapeutic agents and procedures. Although most of the protocols are supported by NCI's Division of Cancer Treatment, several hundred have been provided by other major American and foreign cancer centers.

The growth of the CANCERLIT data base and the usage of CANCERLINE service are shown in figures 1 and 2.

Cancer research information is actively disseminated to more than 7,000 scientists through the ICRDB's Cancer Information Dissemination and Analysis Centers (CIDAC's). Three CIDAC's have been established. The CIDAC for *Diagnosis and Therapy* deals with information on cancer detection, diagnosis, treatment, rehabilitation, and other aspects of clinical oncology. The CIDAC for *Carcinogenesis* relates to chemical, environmental, and physical carcinogenesis, as well as cancer epidemiology. CIDAC for *Cancer Biology* covers the areas of biochemistry, cytology, genetics, immunology, virology, and other cancer-related disciplines. The information products of these facilities are actively disseminated by two major types of service. One is a monthly current awareness service known as CANCERGRAMS and the other is entitled ONCOLOGY OVERVIEWS. CANCERGRAMS are collections of abstracts of newly reported results in specific cancer research topics of special interest to research investigators. About 30 ONCOLOGY OVERVIEWS are published annually.

The ICRDB program also supports several specialized international projects to communicate information to scientists. An International Cancer Epidemiology Clearinghouse, funded jointly with the International Agency for Research on Cancer (IARC) in Lyon, France, and the

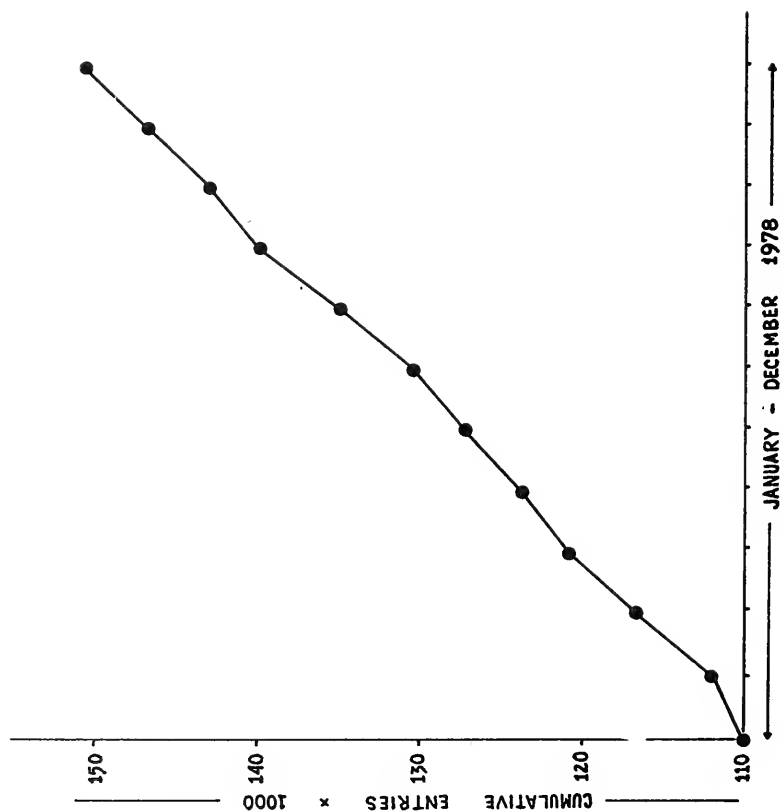


Figure 1. CANCERLIT data base growth.

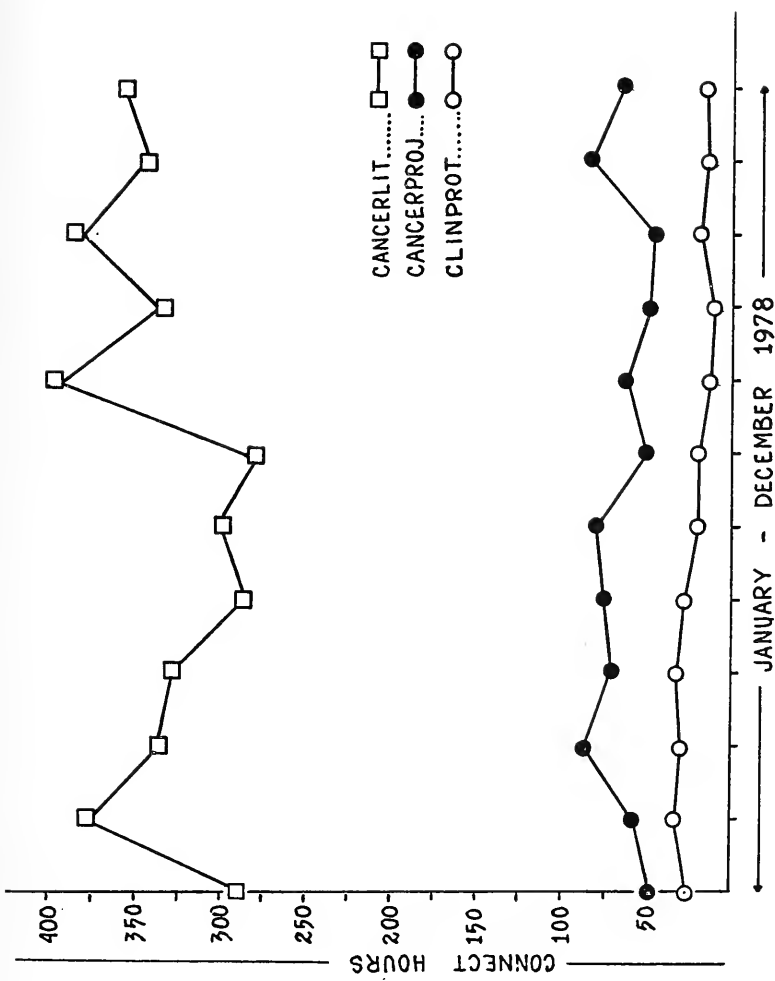


Figure 2. CANCERLINE usage.

German Cancer Research Center in Heidelberg, West Germany, publishes a recurring *Directory of Ongoing Research in Cancer Epidemiology*. The clearinghouse collects, processes, and disseminates detailed research data related to cancer epidemiology and studies of human cancer causation in countries around the world.

With the cooperation and support of the ICRDB program, the World Health Organization (WHO) has developed a series of publications on *The International Histologic Classification of Tumors*, designed to facilitate worldwide adoption of a uniform and standard nomenclature for cancer. Collaboratively with ICRDB, the WHO has developed a coded nomenclature for neoplasms, the *International Classification of Diseases for Oncology* (ICD-O), which provides a detailed code for anatomic sites of neoplasms and their histopathology. The ICD-O has been published in English, Spanish, and Portuguese; Russian, French, and German language versions are in preparation. The ICD-O is designed to be used in tumor registries, cancer data banks, pathology laboratories, and departments of vital statistics so that data on cancer from different countries can be uniformly coded, reported, and analyzed.

In collaboration with the Pan American Health Organization (PAHO), a Latin American Cancer Research Information Project (LACRIP) has been established. PAHO and its regional Library of Medicine (BIREME) identify, collect, and provide CANCERLINE with biomedical literature and summaries of active cancer-related projects in Latin America. PAHO serves as the coordinator for a series of clinical trials being conducted in eight Latin American cancer centers, each of which is linked with an American center, thus assuring that new technology and clinical skills developed in the United States will be disseminated rapidly among the cooperating Latin American centers.

Support is provided to the International Union Against Cancer (UICC) in Geneva which, through its Committee for International Collaborative Activities (CICA), assists the ICRDB in the collection and dissemination of cancer information throughout the world. CICA personnel identify and promote collaborative projects among cancer centers and cancer specialists in different countries. CICA has published an *International Directory of Specialized Cancer Research Treatment Establishments*, containing descriptions of more than 700 cancer centers around the world.

A partially ICRDB-supported center in Japan—the International Medical Information Center—coordinates the screening and collection of cancer-related information from Japan and Asian countries for entry into the CANCERLINE data bases.

The availability of the CANCERLINE system and its use in developing countries is being promoted through a contract with the British Library. This extension of the CANCERLINE service will enable scientists in some 100 developing countries to receive pertinent literature related to their cancer research efforts. They will also be in a position to keep abreast of recent advances in cancer research and cancer treatment.

Of significance is the recent collaborative effort of the ICRDB program and the UICC/CICA leading to the successful implementation of the *International Cancer Patient Data Exchange System* (ICPDES) on a pilot-project scale. The ICPDES could result in the first internationally recognized and standardized tumor registry providing information on (1) cancer patient followup; (2) survival data; (3) demographic data; (4) comparisons and evaluations; and (5) eventual influence on treatment policy.

Seven European cancer centers and four in the United States are participating in a project for the exchange of patient data. Two data centers, one in Europe and one in the United States, will store and analyze the data, currently dealing with four designated cancers: breast, colon and rectal, Hodgkin's disease, and larynx. As of June 1, 1978, the total numbers of eligible cases received per center are as follows:

Center	Cases	Cases To Be Entered	Total
Brussels	110		110
Rotterdam	97	161	258
Milan	228		228
Budapest	134	212	346
Moscow	131	181	312
Bordeaux	13	146	159
M.D. Anderson	362		362
			<hr/> 1,775

The cooperation of the Soviet Union as an active participant in this cancer data/information system is an encouraging sign. Up to this point, the Soviets have been reluctant to join the collaborative communication network established between the ICRDB program and other international institutions.

Scientist-to-Scientist Communication

A means for person-to-person communication between cancer researchers was implemented in 1975, with the acceptance of the UICC proposal to operate two major programs for an effective exchange of information between scientists in the international sphere. These are the International Cancer Research Technology Transfer (ICRETT) program and the International Cancer Research Workshop (ICREW) program.

The ICRETT program provides awards to support brief research activities, usually not exceeding 3 weeks, to enable investigators from two different countries to work jointly on a problem of common interest or meet for intensive discussions and/or demonstrations on significant cancer technology.

The ICREW program provides partial support for workshops that bring together a small number (15 on the average) of cancer investigators from different countries, all of whom are working in the same field of basic, clinical, or behavioral research related to cancer.

Since 1975, ICRETT program awards have been made available to some 250 individual scientists while some 50 workshops were sponsored under the aegis of the ICREW program. From December 7, 1977, to mid-November 1978—the third year of ICRETT and ICREW—15 workshops took place and some 120 ICRETT awards will have been made.

Many of the recipients of ICRETT awards continue to collaborate on projects initiated during their visits to the laboratory of their host. As an example, an Argentine physician working in the area of experimental leukemias spent 3 weeks in the Institute for Scientific Research in Cancer, Villejuif, France. During the brief tenure, he was able to learn several operational steps necessary for somatic cell hybridization and chromosome-gene transfer between cells. As a result of this exposure/training, he is now able to utilize these techniques in his own laboratory in Buenos Aires in analyzing tumor-tumor and tumor-normal cell hybrids.

During a 2½-week visit to the University of Texas Health Sciences Center at San Antonio, a Yugoslav scientist was able to compare his methods with those of his hosts for steroid receptor assay in breast cancer tissue. Because of this interaction, the visiting researcher was able to clarify some methodologic problems and technical difficulties he had been experiencing in his own laboratory. Exchanges such as this are extremely valuable for enabling investigators to standardize techniques and methodologies, thereby ensuring more precise interpretation of data from research in different laboratories on a common problem.

A pathophysiologist from the IIT Research Institute in Chicago was able to observe the histologic criteria used by Japanese researchers (Nagoya City University Medical School) for the classification of chemically induced tumors of the urinary bladder.

The ICRETT and ICREW programs have been well received and are assessed as being scientifically rewarding. Acknowledgement of their value stems from the increasing number of applications in each succeeding year of the programs. The programs have been very successful in promoting and supporting the exchange of research information among scientists from various parts of the world and, in turn, have increased the opportunities for both formal and informal collaborative research activities on the causes, treatment, and prevention of cancer. Without these mechanisms for the exchange of cancer information, prevailing circumstances in the countries of some of the promising scientists might have delayed, by months, the opportunity for learning the most recent results in their fields of scientific endeavor. In slightly more than 2 years, the ICRETT and ICREW programs have enhanced international communication in science and the promotion of important exchanges in science not covered by other research funding mechanisms. In several

instances significant contributions to the cancer literature have resulted from the exchanges.

Bilateral Agreements

The National Cancer Institute has been a party to formal and informal Bilateral Agreements since May 23, 1972, the time of the signing of the U.S.A.-U.S.S.R. Agreement for Cooperation in the Fields of Medical Science and Public Health. Subsequently, additional cooperative programs were initiated between the NCI and the Japanese Society for the Promotion of Science (1974); the Institute of Oncology of Warsaw, Poland (1976) as a segment of the U.S.A.-Polish People's Republic Agreement; the Cairo Cancer Institute (1976) under the aegis of the U.S.A.-Arab Republic of Egypt Agreement; the Ministry of Science and Technology of the Federal Republic of Germany (1976); and, in 1977, with the French Institut National de la Sante et de la Recherche Medicale (INSERM) under the earlier NIH Agreement with INSERM.

In 1978, the NCI entered into its sixth bilateral association with the National Tumor Institute (Milan) and Institute of Experimental Oncology (Genoa) as part of the U.S.A.-Italian Republic Agreement entered into in 1977. Negotiations are in progress for still another cooperative program between the NCI and the National Institute of Oncology (Budapest) under the auspices of the 1978 U.S.A.-Hungarian People's Republic Agreement.

The U.S.-U.S.S.R. Agreement for Cooperation in the Fields of Medical Sciences and Public Health

Six cancer problem areas are being studied jointly under the U.S.A.-U.S.S.R. Health Agreement: (1) cancer chemotherapy and combined modalities treatment; immunology; virology; somatic cell genetics related to neoplasia; cancer epidemiology; and methods of cancer control and the role of cancer centers in cancer control, education, and training.

During 1978, eight scientifically successful meetings of delegations or small working groups were conducted in the areas of cancer virology, mammalian somatic cell genetics, cancer epidemiology, and cancer control cancer centers. The total U.S.-U.S.S.R. cancer program was reviewed in the NCI in September 1978 and further scrutinized during Session Seven of the U.S.-U.S.S.R. Joint Committee for Health Cooperation in Moscow, October 1978.

Forty-seven Soviet cancer specialists visited the United States in 1978 and 25 American scientists were received in the Soviet Union. Some 51 person-months were devoted to these exchanges—40 person-months by the Soviets and 11 by the Americans.

In *cancer chemotherapy*, the results of the study of 71 anticancer preparations were reviewed. The information from these data is the source for our second joint monograph, *U.S.A.-U.S.S.R. Preclinical Anticancer Chemotherapy Test Data and Their Clinical Correlation*. The English and Russian versions of the volume are scheduled for 1979 publication. Ongoing projects in lung cancer were reviewed and agreement was reached to continue studies in the Soviet Union on the treatment of small-cell carcinoma and undifferentiated carcinoma of the lung. The Soviets use combinations of American and Soviet nitrosourea derivatives, surgery, and radiation therapy. Our drug exchange to date has been highly productive—166 anticancer and potential anticancer agents have been exchanged. Additional drugs have been considered for exchange in 1979—three from the Soviets and four from the United States.

During our Fifth U.S.A.-U.S.S.R. Oncology Program Review in September, the Soviet side summarized its work in *cancer immunology* on the immunotherapy of melanoma using BCG immunostimulation alone and in combination with surgery or with chemotherapy. Clinical trials, using four different protocols, have been completed and some significant results have been obtained. The Soviet studies confirm the results obtained in the United States, i.e., chemotherapy plus immunostimulation prolongs the time of melanoma remission. Long-term followup observations will continue. Trials are continuing in the U.S.S.R. using the protocol for C-parvum vaccine in breast cancer patients. New protocols for immunotherapy in various skin melanomas and lung cancer are under consideration.

During their September meeting in Riga, American and Soviet *virologists* expressed satisfaction with their progress. Collaborative effort is continuing in seven topics on the identification, isolation, and characterization of viruses associated with certain cancers as well as those considered to be potentially carcinogenic or playing roles as cocarcinogens. From this research, two findings of significance have evolved: the isolation of a type C virus and the characterization of a type D RNA virus. These findings are detailed in joint scientific publications.

The action on *genetic* systems of two anticancer drugs—5-fluorouracil (USA) and Ftorafur (USSR)—is being studied at the M.D. Anderson Hospital and Tumor Institute (Houston) and the Oncologic Scientific Center (Moscow). Both drugs have comparable cytogenetic activity in that they *damage tumor cell chromosomes* more significantly than they do chromosomes in normal cells. The exchange of biopsy specimens and cell cultures from tumors and rare genetic disorders predisposing to cancer is enabling American and Soviet geneticists to carry out complementary studies on the genetic basis of the disease from country to country.

In *cancer epidemiology*, the success of the Harvard-Tallinn studies has encouraged American and Soviet scientists to continue work on the epidemiology of breast cancer with the expectation of developing additional data on high- and low-risk factors. Joint studies on the estriol-to-estrogen ratio in the urine of young women from Estonia are

nearing completion, and consideration is being given to including Georgian and Kazakh women. Plans for studies on the epidemiology of gynecologic cancer are under review in both countries.

In *cancer control and cancer centers* agreement was reached on methods of classification and a unified terminology for describing non-infiltrated and infiltrated breast carcinomas. Risk factors in breast cancer were agreed to. The use of thermography for *early detection* was considered unreliable at this stage. Criteria for the use of film mammography were established. A uniform questionnaire and procedures have been developed for the study of breast cancer rehabilitation methods in 300 women in each country. Data collection is proceeding. Additional methods have been developed for analysis of data and evaluation of the end results of treatment of breast cancer patients. American and Soviet cancer centers with similar activities have been selected for studying the role of cancer centers in education of professional and public populations.

The American-Soviet cooperative program in cancer affords an outstanding example of an interdisciplinary approach to dealing with a specific cancer site (figure 3). The insidious problem of breast cancer is being studied by American and Soviet cancer therapists, immunologists, virologists, epidemiologists, and cancer control specialists. Such a concerted effort should pave the way for better methods of early detection of the disease, greater accuracy in diagnosis, more effective therapy, and elucidation of fundamental information that should ultimately bring about the control and/or prevention of the disease.

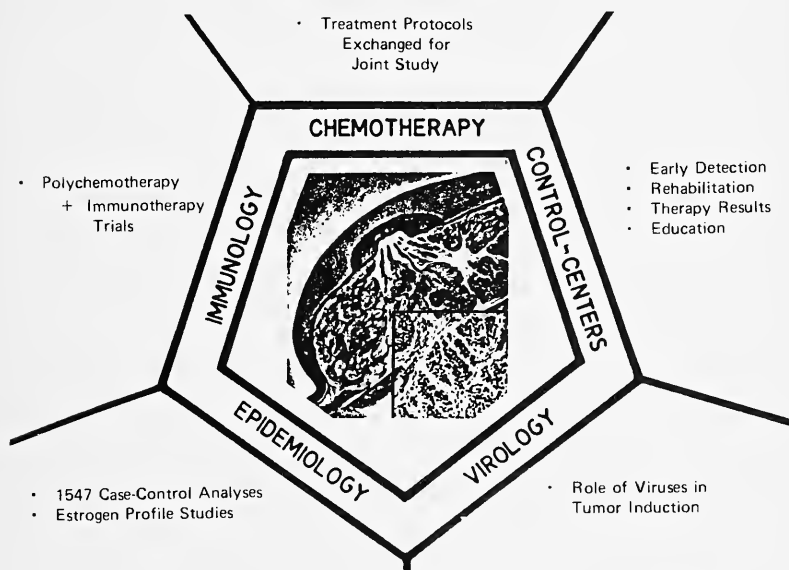


Figure 3. Breast cancer: interdisciplinary approach.

*The Agreement Between the National Cancer Institute
and the Japan Society for the Promotion of Science*

Since the inception of the U.S.A.-Japan Cooperative Research Program in May 1974, some 500 scientists from both countries have attended scientific and planning meetings, served as hosts to visiting delegations, or collaborated in laboratory projects. Conferences have been held on the causation of bladder cancer and on the comparative epidemiology of cancer in the United States and Japan. Nine other major areas of cancer are being explored.

In the *cancer immunology program area*, a meeting on Immunotherapy of Cancer and its Fundamental Basis resulted in an exchange of current information concerning clinical studies on immunotherapy and immunochemotherapy of cancer patients, using immunopotentiators such as mycobacterium and its components. Fundamental studies on the mechanism of immunopotentialiation were discussed.

In the *chemical carcinogenesis program area* a 3-day symposium took place on the Role of DNA Repair and Misrepair in Radiation and Chemical Carcinogenesis in conjunction with the First International Radiation Biology Symposium on Molecular Mechanisms and Genetic Factors in Radiation Carcinogenesis. The scientific sessions were devoted to DNA repair defects in hereditary diseases with high incidence of cancer; genetic and epigenetic factors in radiation and chemical carcinogenesis; and inducible repair and misrepair in carcinogenesis and mutagenesis.

Dialogue continues on the recent advances in both countries in the diagnosis and treatment of *lung cancer*. During the fourth joint symposium, topics discussed were (1) progress in morphology: the updated WHO classification of lung cancer, with special reference to the morphologic subtypes of small-cell and large-cell carcinoma; (2) advances in the immunotherapy of lung cancer; (3) progress in the treatment of small-cell carcinoma, including multidisciplinary treatment methods; (4) treatment of non-small-cell lung cancer, both multidisciplinary treatment and chemotherapy; (5) indications for surgery in advanced lung cancer; and (6) cell kinetics and marker substances: their role for planning and monitoring of therapeutic studies. It is anticipated that these discussions will lead to collaborative activities in lung cancer inasmuch as the incidence rates in both countries are increasing. Efforts in the future will include comparisons of data on clinical results.

In the *breast cancer program area*, a meeting on Hormonal Receptors in Breast Cancer resulted in the exchange of data on the relation of hormones to breast cancer in two different population types. Significant differences were reported in the incidence and prognosis of breast cancer in each country. Japanese and American scientists discussed studies of hormone receptors in their respective populations and correlated these results with histopathology, free interval, and endocrine responsiveness. Similarities and differences were discussed regarding the subcellular biochemical pathways concerned with hormone dependence in the two patient populations.

In the exchanges on *cancer virology*, emphasis is placed on the mechanism(s) of oncogenesis by DNA tumor viruses at the molecular and cellular levels of the host. Discussions focused on recent attempts to identify and to isolate the oncogenic fragments of the viral genomes and also on the function of their gene products. Information was exchanged on the correlation of the recent basic findings in virus research with efforts to determine the etiologic role of DNA viruses in certain types of animal and human neoplasias.

Twelve Japanese and 10 American biostatisticians, *epidemiologists*, and cancer specialists met for a 4-day conference on the effective application of statistical methods to cancer research in order to promote the use of statistics in cancer research. The meeting was a success in that it brought together Japanese and American statisticians and epidemiologists to discuss mutual problems encountered in advancing the status of biostatistics and cancer epidemiology. During a joint symposium on *cancer chemotherapy*, discussions included (1) the design and methodology of phase I and II studies; (2) clinical evaluation of drug analogs; (3) clinical evaluation strategy in specific disease types, namely, lung cancer, breast cancer, gastrointestinal cancer and genitourinary cancer; (4) new drugs, including screening and development, and new drugs in clinical trials; (5) discussion on four classes of drugs, including nitrosoureas, bleomycin, anthracyclines, and fluorinated pyrimidines; and (6) joint cooperation on gastric cancer treatment protocols.

The main purpose of the workshop on *high LET radiation* was to discuss the progress of ongoing cooperation in fast neutron radiotherapy and the development of common clinical trial protocols. Plans were advanced for investigations on the role of hyperthermia, use of radiosensitizers, and other alternatives to high LET radiation therapy.

The major highlight of the *cytology program* was the exchange of two senior pathologist-cytologist investigators. Each will spend an extended period of time conducting joint research in the other's country.

The Joint American-Japanese Steering Committee, during 1978, agreed to restructure the program to four major categories of cancer research: *carcinogenesis*, *cancer biology and diagnosis*, *cancer treatment*, and an *interdisciplinary program*.

U.S.-Polish People's Republic Agreement

Under the Agreement between the United States and the Polish People's Republic for Cooperation in the Field of Public Health, American and Polish scientists visited the Institute of Oncology in Warsaw and the National Research Institute for Mother and Child for exchanges in pediatric oncology, radiation therapy, the leukemias, and carcinogenesis. Polish scientists engaged in research training and cooperative research activities at several American cancer centers in fields that included biochemistry, endocrinology, epidemiology, pharmacology, and cancer treatment.

U.S.-Arab Republic of Egypt Agreement

In the program sponsored by the National Cancer Institute and the Cairo Cancer Institute, Egyptian cancer specialists and NCI staff are working together on two bladder cancer programs in which there is a relationship to bilharzial (schistosomiasis) infection among Egyptians. The joint study has established that the use of hexamethylmelamine reduces the size of the tumor for subsequent surgical intervention.

NCI-Ministry of Science and Technology of Germany

The program being developed under the NCI-German Ministry of Science and Technology Agreement has produced activity in the area of automated cytology technology for use in cervical cancer diagnosis and a potential application to the detection of cancers of the oral cavity. Negotiations are under way to expand this bilateral program to include (1) the testing of chemical carcinogens; (2) determination of the mechanism(s) of action of carcinogenesis; and (3) study of the metabolism carcinogens.

NCI-INSERM (Republic of France) Cancer Program

Under the agreement with the Institut National de la Sante et de la Recherche Medicale of France, planning meetings have been held for collaborative research and for the exchange of scientists in the areas of viral oncology, hormone regulation in cancer, and treatment research. Collaborative experiments have been undertaken on topics such as cell transformation by viruses; the genetics of RNA tumor viruses; cellular antigens; hormonal regulation of receptor synthesis; pharmacokinetic studies of 5-fluorouracil; and clinical trials using high dose methotrexate protocols, cis-platinum derivatives, FAM chemotherapy, and the combination of chemo- and immunotherapy.

U.S.-Italian Republic Agreement

The NCI and institutes of the Italian Ministry of Health will cooperate in cancer treatment research (drug development and clinical trials), carcinogenesis, and epidemiology.

U.S.-Hungarian People's Republic Agreement

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The interest in joint efforts between the NCI and the Hungarian National Institute of Oncology includes experimental therapeutics,

experimental pathology, and immunology, with emphasis on leukemia and hematologic research.

Informal Exchanges With the People's Republic of China

In September 1977 there were 3 senior NCI scientists among the 11 Americans invited by the Committee on Scholarly Communication with the People's Republic of China (PRC) National Academy of Sciences to visit various cancer research institutions and cancer hospitals in the PRC. During the 3-week visit, the American delegation had opportunities to discuss aspects of clinical treatment of various types of cancers, the epidemiology of cancer, and problems of basic research being supported in the cancer centers.

Reciprocally, a delegation of 15 Chinese cancer specialists was hosted by the American Cancer Society in April 1978. The delegation visited several American cancer centers, in addition to spending 2 days at the National Cancer Institute. An extensive program on clinical and basic research in cancer was planned for the visitors, among whom were radiologists, epidemiologists, clinicians, and basic cancer specialists representing leading Chinese centers in Peking, Shanghai, and other cities.

In the purview of the NCI, potential cooperation with the PRC in cancer studies could include (1) geographic epidemiology; (2) developmental therapeutics; (3) biochemical pharmacology and immunology; and (4) cancer biology, especially in vitro testing and somatic cell genetics related to neoplasia.

Collaborative Research With Visiting Foreign Nationals

As in previous years, the NCI Visiting Scientist Program has provided opportunities for young foreign scientists, as well as established researchers, to engage in cancer research with their American colleagues and share in their scientific experience. During the past year, the NCI hosted 155 visiting scientists representing 27 nations of the world. The majority of the visitors were young researchers who came to acquire advanced training and experience in the laboratories of senior NCI investigators. Eighteen foreign scientists were appointed as *Experts*, having obtained temporary senior positions for the conduct of independent research or for collaboration with senior NCI staff members on extant projects in their scientific specialties. Sixteen foreign scientists had temporary appointments as *guest workers*, receiving financial support from their home institutions or private or public foundations.

Table 1 shows the number of such visitors and their countries of origin.

Table 1. Scientists From Foreign Nationals Visiting the NCI, FY 1978

Countries of Origin	Visiting Scientists	Experts	Guest Workers
Argentina	1	--	--
Australia	4	2	1
Belgium	4	1	1
Brazil	1	--	--
Bulgaria	--	--	1
Canada	1	2	--
China, Republic of (Taiwan)	4	--	--
Egypt	2	--	--
Finland	1	--	--
France	1	--	--
Germany, Fed. Rep. of	3	--	1
Greece	2	--	1
Hong Kong, B.C.	1	1	--
India	21	1	1
Ireland	1	--	--
Israel	6	--	--
Italy	14	--	--
Japan	24	3	2
Malaysia	1	--	--
Mexico	1	--	--
Netherlands	2	--	--
Poland	1	--	--
Portugal	1	--	--
South Africa, Republic of	1	--	--
Spain	1	1	1
Switzerland	3	--	--
United Kingdom	12	3	1
Alien Residents or Immigrants	<u>40</u>	<u>4</u>	<u>1</u>
Total	154	18	11 = <u>183</u>

These activities have been most effective in the sharing of scientific information and the transfer of technology. Foreign scientists have been provided with unique opportunities for the development of a potential for sound research careers or improvement of existing skills in the scientific method. When a foreign scientist has been directly involved in NCI programs and has been exposed to disciplines involved in individual and coordinated projects, he is better equipped for solving problems within his competence and has greater appreciation for the expertise required to study the complexities of the cancer process. Close working contact between NCI scientists and those of foreign institutions will tend to improve and enhance technical and personal cooperation between individuals and groups.

International Contracts and Grants

During FY 1978, the NCI awarded 92 contracts and 45 grants to principal scientists conducting basic and applied research in institutions of 20 nations of the world. The financial outlay of the NCI for these research activities is estimated to be about \$13,500,000 of FY 1978 funds, or approximately 1.5 percent of the NCI budget. Each of the projects supported in foreign countries is applicable and contributory to the goals of the NCI research thrusts. A profile of the NCI-supported international research and its emphasis is indicated by the following scientific disciplines:

- Biochemistry and immunochemistry
- Cancer biology
- Carcinogenesis
- Drug development
- Diagnosis
- Epidemiology
- Immunology
- Organ site cancers
- Treatment research
- Viral oncology
- Conference grants
- Information service
- Planning and development

In the Division of Cancer Biology and Diagnosis emphasis is placed on fundamental immunology and immunotherapy. Research activities are related, in general, to the immune response to tumors, tumor antigenicity, drug-modified antigens, immunopotentiators, and cellular systems that might be established as biologic markers for a given cancer. The cancer problem areas, the number of projects/contracts, the funding per program area, and the distribution of contracts and funds per country are shown in table 2.

Research being conducted for the Division of Cancer Treatment relates, principally, to the characterization of anticancer agents; the search for potential anticancer agents from natural sources such as microbial and plant; and the synthesis, screening, and testing of compounds developed in foreign laboratories. Clinical trials are conducted on specific cancers such as tumors of the brain. Support is provided for a WHO regional center in Milan, Italy, which coordinates clinical studies on the treatment of malignant melanoma, an effort involving a number of countries including the United States and the Soviet Union. The fields of emphasis and distribution of NCI resources toward foreign research in cancer treatment are shown in table 3.

**Table 2. Division of Cancer Biology and Diagnosis Contracts
to Foreign Institutions, FY 1978**

Program Areas	No. of Contracts	Total Amounts
Immunology	23	\$1,403,746
Cancer biology	7	566,654
Breast cancer	<u>3</u>	<u>178,937</u>
	33	\$2,149,337

Countries	No. of Contracts	Total Amounts
Australia	3	\$ 188,781
Austria	2	117,000
Finland	4	167,080
Israel	13	1,047,097
Italy	1	67,000
Netherlands	2	51,275
Sweden	4	235,000
United Kingdom	3	205,113
West Germany	<u>1</u>	<u>70,991</u>
	33	\$2,149,337

**Table 3. Division of Cancer Treatment Contracts
to Foreign Institutions, FY 1978**

Program Areas	No. of Contracts	Total Amounts
Drug development	8	\$ 945,187
Treatment research	9	703,135
Drug research	<u>1</u>	<u>304,430</u>
	18	\$1,952,752

Countries	No. of Contracts	Total Amounts
Belgium	2	\$ 260,760
Canada	2	298,742
Italy	6	729,246
Japan	2	199,000
Netherlands	1	73,151
Uganda	1	25,000
United Kingdom	<u>4</u>	<u>366,853</u>
	18	\$1,952,752

Foreign research activities in carcinogenesis, cell biology, epidemiology, and virology-genetics are of relevance to the research thrusts of the Division of Cancer Cause and Prevention (DCCP). Importance is ascribed to enzyme-induced chemical carcinogens, N-nitroso compounds, and the polycyclic hydrocarbons, respectively, in these areas. Information is needed on the preservation of biochemical mutants, mammalian transport systems, and tissue interacting factors. Morbidity surveys, case control studies, seroepidemiology, risk data, and cancer incidence rates in countries other than the United States are essential. Knowledge is required on the induction of genetic aberrations and their possible relationship to cancer as well as the role of viruses as suspect or potential carcinogens. The effort of DCCP with scientists in foreign laboratories is summarized in table 4.

Table 4. Division of Cancer Cause and Prevention Contracts to Foreign Institutions, FY 1978

Program Areas	No. of Contracts	Total Amounts
Carcinogenesis	20	\$2,437,196
Epidemiology	7	865,569
Cancer biology	1	83,000
Pharmacology	1	85,000
Immunology	1	49,500
Viral oncology	4	785,270
	<u>34</u>	<u>\$4,305,535</u>

Countries	No. of Contracts	Total Amounts
Canada	4	\$ 441,016
Colombia	2	213,514
Israel	5	813,921
Italy	1	85,000
Japan	3	162,704
Netherlands	3	312,500
Norway	1	7,800
Sweden	2	392,000
United Kingdom	7	512,377
West Germany	1	108,120
International Agency (IARC)	5	1,256,583
	<u>34</u>	<u>\$4,305,535</u>

The contracts effected through the Office of the Director, NCI, are listed in table 5. Five of the seven projects relate to the ICRDB program.

**Table 5. Office of the Director Contracts
to Foreign Institutions, FY 1978**

Program Areas	No. of Contracts	Total Amounts
Carcinogenesis	1	\$ 150,000
Epidemiology	1	115,049
Information science	4	973,997
Planning and development	<u>1</u>	<u>1,418,869</u>
	7	\$2,657,915

Countries	No. of Contracts	Total Amounts
Japan	1	\$ 150,000
United Kingdom	2	1,578,869
IARC (France)	2	265,049
UICC (Switzerland)	<u>2</u>	<u>663,997</u>
	7	\$2,657,915

Table 6 provides similar data on the number of research grants awarded to scientists in foreign countries for meritorious studies in areas of interest to the NCI and its mission.

Table 6. NCI Research Grants to Foreign Institutions, FY 1978

Program Areas	No. of Grants	Total Amounts
Cancer biology	3	\$ 156,924
Carcinogenesis	6	262,433
Diagnosis	1	15,401
Drug development	2	46,255
Treatment research	14	809,741
Epidemiology	1	24,600
Immunology	11	673,557
Pharmacology	1	47,555
Viral oncology	4	154,715
Conference grants	<u>2</u>	<u>131,162</u>
	45	\$2,322,343

Countries	No. of Grants	Total Amounts
Australia	4	\$ 164,395
Belgium	1	298,286
Canada	14	574,785
Denmark	1	39,400
Finland	1	38,000
France	1	50,000
Israel	8	387,058
Japan	1	45,024
Korea	1	11,005
South Africa	1	72,397
Sweden	2	230,358
United Kingdom	7	238,882
West Germany	2	73,411
UICC (Switzerland)	1	99,162
	45	\$2,322,163

The relationship with international institutions and organizations and their scientists has been mutually advantageous in providing opportunities for furthering our understanding of the causes of cancer, its treatment, and its control and/or prevention. Certainly, the expertise of foreign researchers and the results of their investigations are relevant to the NCI goal of improving cancer treatment and significantly reducing the incidence of human cancer.

Summary

The foregoing description of the international activities of the National Cancer Institute delineates the NCI impact on the effort against cancer by a seeming consortium of nations. Reciprocally, those nations collaborating with the NCI in the "war on cancer" are making significant contributions to the missions of the NCI for the peoples of America. Advancing the thesis of international cooperation a bit further, the products of this research effort are being applied toward the improvement of cancer care mechanisms or systems in those countries where the socioeconomic environment seems to preclude such advances through autonomous research endeavors. By continuing, and even expanding, its role in collaborative international research, the NCI will understand better the relationship between cancer patients of the world and the differing biologic, economic, sociologic, and technologic conditions that impinge upon their immediate being. As each new piece of information is added to existing knowledge related to the cancer-disease-complex, its cure and prevention could be accelerated. This becomes even more pragmatic when we consider that a disease is a biologic aberration—abnormal alterations in a cell, a molecule, an organ, or an

entire physiologic system. A *disease*, therefore, can be understood in scientific and objective terms. But the changes in biologic processes that create the disease, cancer, are not fully understood. Thus, it is mandatory that the momentum continue. Eventually, early detection will be possible, more efficient controls and/or cures will be instituted and, ultimately, prevention may be possible.

National Eye Institute

Introduction

The National Eye Institute conducted an active international program in FY 1978. Essentially the Institute's international activities fall into two categories: (1) the conduct of research by investigators around the world where high level expertise is available and unique research opportunities exist; and (2) the provision of advice and consultation to various U.S. Government agencies, such as the Office of International Health, PHS; the Office of the Secretary, HEW; the Agency for International Development; and the State Department, concerning eye disease and the prevention of blindness. As one of the few sources of expertise in eye disease and eye care in the U.S. Government and certainly the principal referral point for this information, the National Eye Institute is frequently called upon by other Government agencies.

Background

Part F, Section 453 of the Public Health Service Act provides the following legislative mandate to the Secretary, HEW:

The Secretary shall, through the National Eye Institute established under this part, carry out the purposes of Section 301 with respect to blinding eye disease and visual disorders associated with general health and well-being, including the special health problems and requirements of the blind and the mechanism of sight and visual function.

In FY 1978, the National Eye Institute direct budget for international activities was:

Research Grants	\$500,000
Direct Consultations	\$ 25,000

Major Programs and Activities

On May 2, 1978, President Carter made the following official statement regarding international health:

We will put special emphasis on providing clear drinking water, basic sanitation, basic immunizations and efforts to prevent and treat blindness.

Secretary Califano of HEW followed up on this Presidential priority with the following message to the World Health Assembly meeting in May 1978 in Geneva, Switzerland:

We will support worldwide efforts to prevent and treat blindness. The stark fact is that 80 percent of blindness is preventable or curable. But unless we can expand prevention and treatment programs, the number of blind people throughout the world will continue to increase . . .

The National Eye Institute has been requested by the Office of International Health, HEW, and the Fogarty International Center, NIH, to lend its expertise to shaping U.S. efforts that will lead to the realization of the objectives contained in these two statements. Additionally, the NEI in carrying out its basic mission in vision research is supporting a number of vision research projects around the world on an individual basis and through bilateral agreements with foreign countries. During FY 1978, NEI engaged in the international programs summarized below by program area.

Collaboration and Consultations With the World Health Organization (WHO)

The Director, National Eye Institute has been appointed as a member of the WHO Programme Advisory Group for the Prevention of Blindness. The major aims of this group are to advise on the development of a program including priority setting, project evaluation, and consultantships. In establishing a separate Programme for the Prevention of Blindness on January 1, 1978, WHO has made a major commitment to serve as promoter, or catalyst, for national and local efforts to alleviate the overburden of world blindness. The WHO activity is directed at:

1. Assessment of nature and extent of the problem;
2. Formulation of national or regional plans, programmes and projects;
3. Collection, collaboration, and distribution of relevant data;
4. Organization and management of training activities such as seminars, meetings, training courses, including the preparation and provision of teaching aids;

5. Advisory services by short-term consultants, and possibly of personnel for longer periods.

Additionally, in FY 1978 the Director, NEI, participated as an official member of the U.S. delegation to the annual World Health Assembly of the WHO. Discussions and consultations with health ministers of many countries and WHO officials were held regarding the development of prevention of blindness activities.

Future Plans

The Institute plans to continue active collaboration and participation in the WHO Programme for the Prevention of Blindness. In 1979 it is expected that the NEI will provide modest funding to WHO for the support of projects aimed at

1. Obtaining sound epidemiological data on the prevalence of visual impairment and blindness from all causes;
2. Evaluating available health technologies and promoting programs to make the most cost/effective of these available to affected populations; and
3. Stimulating programs of research into blinding eye diseases for which there is no known satisfactory treatment and controlled, clinical evaluation of findings which appear to be effective.

Finally, the NEI intramural program in Bethesda is making plans to be designated as a WHO collaborating center.

International Agency for the Prevention of Blindness

During 1978, the National Eye Institute continued its cooperative efforts with the International Agency for the Prevention of Blindness (IAPB). The IAPB's mission is to spread the message of the extent and distribution of world blindness, particularly to developing nations, since most preventable blindness occurs in these nations. Developed nations can provide resources and expertise to prevent world blindness and improve their own prevention activities. Most importantly, the IAPB must create the will for these nations to act in their own behalf and for the benefit of people everywhere who are potential victims of avoidable and curable blindness. Private voluntary U.S. organizations that are members of the IAPB are the Helen Keller Institute, the National Society to Prevent Blindness, and the International Eye Foundation. Over 47 countries have national committees that are members of the IAPB.

National Eye Institute staff participated in the First General Assembly of the International Agency for the Prevention of Blindness

held in Oxford, England, on July 8, 1978. The assembly was highly successful in promoting international interest and support for attacking the world's major causes of blindness.

FY 1979 Plans

The NEI will continue to serve as an active participant in this organization and encourage private U.S. voluntary organizations to play a more active role in this group.

U.S.-U.S.S.R. Collaboration

Under the U.S.-U.S.S.R. Medical Science and Public Health Agreement, vision research has been recently assigned the same high priority as afforded other major ongoing U.S.-U.S.S.R. collaborative health research efforts in cancer, cardiovascular diseases, artificial heart, environmental health, schizophrenia, arthritis, and influenza and acute respiratory diseases. This collaboration was initiated a few years ago by an exchange of visits between the Director, NEI, and Dr. Mikhail M. Krasnov, Director of the All-Union Scientific Research Institute of Eye Diseases of the Soviet Ministry of Health. Subsequent informal contacts by Drs. Kupfer and Krasnov have resulted in identifying specific research projects and scientists who would initially participate in a vision research exchange program. Detailed plans were developed at the Seventh Session of the U.S.-U.S.S.R. Joint Committee for Health Cooperation held recently in Moscow. These call for initial projects in laser treatment of glaucoma, in research on retinal degenerations, and in studies of cataract.

Also in FY 1978, Dr. Elmer Ballintine, Clinical Director, NEI, attended a symposium in the U.S.S.R. on "The Pathogenesis and Treatment of Hereditary Tapetoretinal Dystrophies" under the individual exchange program of the U.S.-U.S.S.R. Medical and Public Health Agreement. Presentations concerning a new treatment for Retinitis Pigmentosa (RP) with a drug called ENCAD were of particular interest. RP, an important cause of visual disability and blindness, has a devastating impact early in life on those afflicted. In general, the results showed that, despite years of testing in the U.S.S.R., ENCAD's benefits are inconclusive. Individual case reports of improvement following treatment were unconvincing.

International Vitamin A Research Center

A workshop held at the NEI in FY 1977 recommended that the Institute pursue several high-priority research opportunities concerning the relationship of vitamin A to malnutrition blindness, a serious problem in developing countries. During the past decade, many governments

throughout the world have expended significant time and money in distributing vitamin A capsules to combat malnutrition blindness (primarily xerophthalmia and keratomalacia) diseases that severely affect the cornea and are a leading cause of visual impairment and blindness worldwide. Recently vitamin A food supplementation also has been used. Yet the value of these approaches has not been scientifically validated. Very little reliable research data exist on such subjects as: (1) the interdependence of protein supplementation and vitamin A utilization; (2) the best dosage to increase vitamin A blood levels; (3) the most effective approach to increasing retinal-binding protein in the serum of malnourished children; and (4) the possible role of collagenase in keratomalacia. Despite the scientific information available on the biochemistry and physiology of vitamin A in the normal individual, little is known about vitamin A in the protein/calorie deficient child.

The Office of Nutrition in the Agency for International Development is interested in supporting the establishment of a research center to reinforce the following NEI workshop research opportunities:

1. Epidemiology — the relationship of vitamin A deficiency and protein/calorie malnutrition to keratomalacia/xerophthalmia and diarrheal disease in populations at risk.
2. Diagnosis — morphological studies of the effects of vitamin A deficiency on the cornea. Surprisingly, no such studies have yet been conducted.
3. Nutrition — studies of how carotene and retinol are absorbed in affected children with protein/calorie deficiency.
4. Biochemistry — a wide range of studies of the biochemistry of vitamin A in affected patients; e.g., the biochemistry of tissue vitamin A receptors, glycoproteins of the cornea, estimation of liver vitamin A stores, etc.
5. Prevention/Treatment — the best and most cost effective method of rapid vitamin A therapy and of long-term control through treatment, nutrition and education.

To carry out this research, the consultants recommended that a center be established for study of keratomalacia in an area of high patient density and, if possible, in conjunction with an already ongoing program. Two possible locations for the center are Dacca, Bangladesh, and San Salvador, El Salvador. At least one other country will be visited before a final decision is made.

U.S.-Japan Cooperative Agreement

The U.S.-Japan Memorandum of Understanding (MOU) on Vision Research became effective April 1, 1976, for 3 years. The MOU provides for an exchange of scientists program sponsored by the National Eye Institute and the Japan Society for the Promotion of Science. Two

scientists per year from each country may be selected for the exchange—one short-term (2 weeks to 3 months) and one long-term (3 months to 1 year). Plans are under way to renew the U.S.-Japan Cooperative Agreement for a second 3-year period.

The MOU objectives are to foster better communication and interaction between Japanese and U.S. vision research scientists; to broaden the base of vision research through cooperative efforts; and to better utilize existing resources for vision research in both countries.

During 1978, Dr. Thomas G. Ebrey spent 3 months at Kyoto University studying the retinal-protein interaction in visual pigment and the analogous pigments; Dr. Mitsuo Ikeda spent 3 months visiting several laboratories throughout the United States pursuing his studies into physiological optics and visual information processing, specifically in the field of visual pattern perception, color vision and visual sensitivity; and Dr. Naohiro Ishii is spending the better part of 1 year at the Brain Research Institute of the University of California studying analysis and information processing of electrical activity of the brain, pattern recognition, and cybernetics.

In FY 1978, Dr. Kanjiro Masuda spent 1 year at Yale University working in uveitis research, and Dr. Motohiko Murakami spent 3 months visiting several laboratories across the United States teaching a new technique in micro-electrode methods. Also, Dr. Duco Manasaki from the Bascom Palmer Eye Institute spent 1 year at the Tohoku University working in the area of retinal protein interaction in visual pigment and analogous pigments. Dr. William H. Miller spent 2 weeks visiting the St. Marianna University and the Iwate University lecturing on factors influencing visual acuity in the retinas of man and birds and on structures with dimensions near wavelengths of light as intraocular filters.

Today as many as 40 million people are blind. There is a critical need and well-established opportunity to prevent or treat much of this blindness. The National Eye Institute can play an important role in providing technical and medical advice to the U.S. Government's policy-makers concerning the desirability and possible nature of U.S. participation. Also, the NEI can help insure that the most cost-effective new approaches are utilized in an international program for the prevention of blindness by evaluating new technologies and conducting clinically relevant research.

National Heart, Lung, and Blood Institute

Introduction

The National Heart, Lung, and Blood Institute's international programs and activities represent an undertaking in the best tradition of medicine which recognizes no national boundaries in its quest for

relieving human suffering. During FY 1978, the Institute continued to expand its international activities and contacts, and a series of meetings were held with officials from other countries to explore new opportunities of mutual interest.

The problems of heart, blood vessel, lung, and blood diseases and problems related to blood resources are not unique to the United States. They are shared to a greater or lesser degree by all nations, industrialized as well as developing countries. Table I shows selected statistics comparing the United States with other countries in terms of trends in cardiovascular disease, the number one cause of death.

**Table 1. Trend in the Death Rate for Coronary Heart Disease
Selected Countries, 1969-73
Males Age 45-54 Years**

Country	Difference in Death Rate	Rate Per 100,000 Population	
		1969	1973
United States (white)	- 28.3	341.2	312.9
Finland	- 17.1	427.3	410.2
Austria	- 0.4	146.7	146.3
Italy	+ 0.6	112.9	113.5
Netherlands	+ 2.5	188.8	191.3
Switzerland	+ 4.1	103.4	107.5
German Fed. Rep.	+ 9.3	146.4	155.7
Hungary	+ 21.5	142.8	164.3
Sweden	+ 30.1	126.0	156.1
Norway	+ 31.1	191.5	222.6
England and Wales	+ 31.6	254.9	286.5
Denmark	+ 31.9	159.5	191.4
Northern Ireland	+ 43.2	318.9	362.1
Scotland	+ 43.5	329.2	372.7

A highlight of 1978 that has gained worldwide attention is the Institute's report on the significant decline in the previously unchecked epidemic of U.S. deaths from cardiovascular disease (figure 1). This has occurred in both of the major categories: heart attacks and stroke. This decline is steeper than that for other diseases. It is particularly noteworthy in view of the increases in cardiovascular death rates for most other nations, industrialized and developing, over the same period of time. At a recent conference on the decline in cardiovascular deaths, it was predicted that the death rate from heart and artery disease could be cut in half by the year 2005. There is reason to believe that the National Heart, Blood Vessel, Lung, and Blood Program mandated by the President and Congress in 1972, and implemented by the Institute, has played a pivotal role in bringing about these positive trends in the

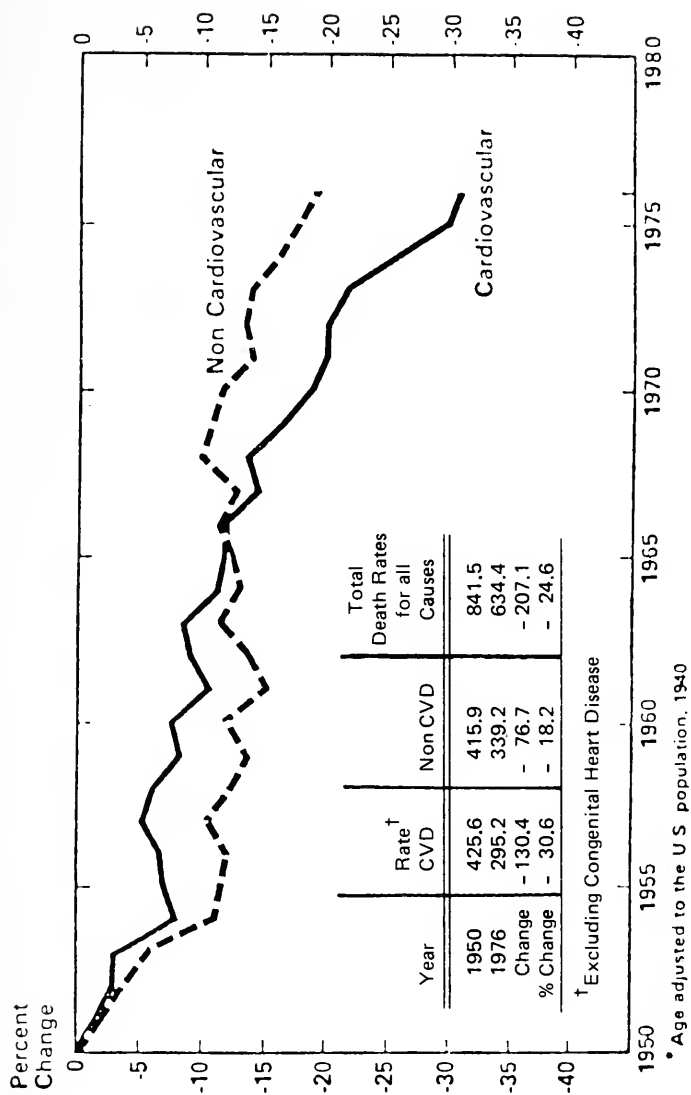


Figure 1. Percent decline in death rates since 1950 for cardiovascular and noncardiovascular diseases.

health of the people of the United States. In 1978 alone 200,000 more heart deaths would have occurred, had death rates stayed at the same level as in 1968.

The experience of the United States has stimulated other nations to try to duplicate the positive results achieved in our country. Many of the Institute's joint meetings with international scientists during the past year focused on how the Institute can best collaborate with other nations to bring about similar results while at the same time obtaining new knowledge about the relative contributions of specific factors in causing the changes observed in the United States. This knowledge will be valuable in further accelerating positive trends in the United States. There is still far to go before the United States approaches the much lower cardiovascular death rates of nations such as Japan, Italy, and Yugoslavia.

Developing countries are also interested in stemming the epidemic of heart and artery disease before it becomes a major economic and health problem. This interest is evident from the requests for advice received by the Institute in FY 1978. International trust in the Institute's approaches and programs is also exemplified in the appointment of the Director, National Heart, Lung, and Blood Institute, as adviser to the World Health Organization (WHO) in the development of long-range programs in cardiovascular disease.

The decline in cardiovascular death rates in the United States has been attributed to a number of factors. The relative roles of these factors are currently under study. Eating and smoking habits of Americans changed considerably during the past decade. A new emphasis on hypertension control was also initiated. The per capita consumption of eggs, milk-fat products, and lard declined significantly as Americans sought to avoid foods containing cholesterol. At the same time there was a decline in the amount of tar and nicotine in cigarettes and a 25 percent reduction in male smokers in all age groups 21 and over in the period 1964 to 1975.

During the past year scientists from other nations showed particular interest in joint international activities related to the so-called major cardiovascular risk factors: hypertension, hyperlipidemia, and smoking. "Hypertension Etiology, Treatment, and Prevention" was approved as a new program area within the U.S.-U.S.S.R. joint exchange in cardiovascular diseases. The collaboration was initiated with a Joint U.S.-U.S.S.R. Symposium on Hypertension held in Sochi in June 1978. A Joint U.S.-F.R.G. Memorandum of Understanding was signed with the Federal Republic of Germany for collaboration on hypertension and arteriosclerosis. A Joint U.S.-F.R.G. Workshop on Hypertension and Arteriosclerosis was held in Heidelberg in August 1978, with followup discussions in Bonn with representatives from the three government agencies responsible for relevant health research programs. Representatives from F.R.G. have requested U.S. collaboration in developing and sharing data on epidemiological studies and risk factor intervention

programs. A Joint Memorandum of Understanding was also negotiated with the Republic of Italy for joint collaboration on the prevention of heart disease. Followup planning meetings were held for a Joint U.S.-Italian Workshop on "Cardiovascular Risk Factors" in Rome in December 1978.

During FY 1978, the National Heart, Lung, and Blood Institute continued programs of joint collaboration with the Soviet Union in the seven previously approved program areas. Collaborative activities continued with scientists in Israel, Yugoslavia, Poland, Great Britain, France, Egypt, Japan, and WHO representatives. The Institute also funded a number of fellowships, contracts, and research grants to investigators in other countries and received visiting scientists from many nations.

Major Programs and Activities

The Institute's international programs and activities are carried out within the Institute's mandates under the National Heart, Lung, and Blood Program. There is no separate legislative authority for these activities beyond those governing HEW and PHS operations, nor is there a separate budget line item for international programs. Operating funds from the Office of the Director, NHLBI, are used for international programs. Funds may also be drawn from line research budget categories, depending upon the project.

The direct costs for NHLBI international activities are summarized in table 2. Under the bilateral agreements, each side pays for the travel of its scientists to the other country. The receiving country pays all expenses for U.S. scientists traveling within the host country and for the facilities, personnel, equipment, and supplies needed for joint studies. The U.S. side pays for reciprocal arrangements within the United States.

U.S.-U.S.S.R. Health Exchange in the Cardiovascular Area

A Joint U.S.-U.S.S.R. health exchange in Cardiovascular Diseases was initiated in 1972 through a bilateral health agreement signed by the U.S. Secretary of State and the U.S.S.R. Minister of Health. The agreement was renewed in 1977 for 5 years.

Four areas of joint collaboration were approved by the U.S.-U.S.S.R. Joint Committee in 1972: Pathogenesis of Arteriosclerosis; Management of Ischemic Heart Disease; Myocardial Metabolism; and Congenital Heart Disease. Two additional areas were approved in 1973: Sudden Death; and Transfusion of Blood, Its Components, and Prevention of Hepatitis with Particular Reference to Cardiovascular Surgery. A seventh area was added in 1978: Hypertension Etiology, Treatment, and Prevention. Cooperation on Artificial Heart Research and Development was initiated in 1974 under a separate agreement signed by Kissinger and Gromyko. This agreement was also renewed in 1977 for 5 years.

**Table 2. National Heart, Lung, and Blood Institute
International Activities
Direct Costs FY 1978**

	Number	Countries	<u>Funds Paid</u> (in dollars)
Fellowships	3	Canada Sweden France	39,776
Contracts	12	Canada United Kingdom Israel	2,554,371
Grants	8	Argentina Canada Denmark Sweden United Kingdom	349,540
Total Awards	23		2,943,687
Bilateral Agreements*		Funds expended in the United States	420,642

*Collaborating countries pay for costs in their own country.

Heart disease is the principal cause of death in both the Soviet Union and the United States. It is an area of intense public and scientific interest in both countries. Significant progress was made during FY 1978 in terms of further developing joint areas of research, resulting in exchange of information and data, and publication of papers on joint research.

During the past 6 years of cooperation, the total number of individuals exchanged in the eight cardiovascular areas was 339: 214 U.S. and 125 U.S.S.R. specialists. The total number of man-months was 237, counting one man-month as 30 days exchange in either country: 113 for the U.S. and 124 for the U.S.S.R. More than 100 U.S. and Soviet institutions have participated in the exchange, more than 60 in the U.S. and more than 40 in the U.S.S.R. Ten joint symposia were held. The proceedings of nine symposia were published (or are in press) in English and in Russian. The proceedings of the latest symposium, held in June 1978, are being prepared for publication. A total of more than 300 scientific reports, abstracts, and related articles have been published under the aegis of the joint U.S.-U.S.S.R. exchange in the cardiovascular area.

Pathogenesis of Arteriosclerosis. Arteriosclerosis, the subject of joint epidemiological studies in area 1 of the Cardiovascular Exchange,

is the most common cause of cardiovascular disease. Directly or indirectly it is responsible for more deaths in the United States and the Soviet Union than any other disease.

The U.S.-U.S.S.R. Lipid Research Clinics (LRC) program is a unique endeavor in conducting a binational multidisciplinary, multi-clinic collaborative research program. This program particularly focuses on the metabolism and epidemiology of plasma lipids and lipoproteins as they relate to the atherosclerotic disease in total populations. During FY 1978 this program maintained its well established high level of success. Some of the results of the joint studies have been published and a number of joint publications are in preparation. Two joint working meetings and two joint steering committee meetings were held in FY 1978.

The initial agreement stated that the U.S.-U.S.S.R. study would include men between the ages of 40-59 years. This study has now been completed and the joint analysis is in progress. On the U.S. side, the Lipid Research Clinics program studied approximately 33,000 individuals during the initial phase (phase 1) of the study and about 4,000 in the second, more specialized phase (phase 2). On the U.S.S.R. side, 8,000 individuals were studied in Moscow and Leningrad during phase 1, and approximately 2,000 during phase 2.

Interesting new biochemical data have been generated as a result of the cooperation. Last year significant differences were discovered between populations studied in Leningrad and the United States, especially in the blood levels of high density lipoproteins. During FY 1978 these findings were further delineated. This is an important area of new research which has a following the world over. The reason for the interest in high density lipoprotein is that high levels of this lipoprotein are generally associated with longevity and decreased risk of heart disease. The U.S. levels of this lipoprotein are lower than those in Leningrad and, to a lesser extent, than those in Moscow. The findings may have implications for the U.S.-U.S.S.R. joint effort to lower the risk factors in arteriosclerosis.

Important new findings from the U.S.-U.S.S.R. joint studies in the LRC's were reported at the U.S.-U.S.S.R. Joint Symposium on Hypertension in Sochi in June 1978. The data show that, in the populations studied, U.S.S.R. men ages 40-59 have higher levels of blood pressure than U.S. men of comparable age. The prevalence of high blood pressure was two to three times greater in U.S.S.R. than in U.S. white men. Also, the prevalence of hypertension was higher in hyperlipidemic men than in random sample examinees in both the U.S. and U.S.S.R.

During FY 1978, agreement was reached on a mortality followup study of men ages 40-59 years screened during phase 2 of the original joint study, and a sample of those screened during phase 1. Agreement was also reached on expanding the U.S.S.R. prevalence studies to other population groups including men and women, ages 20-69, residing in districts of Moscow and Leningrad other than those included in the earlier joint studies. Also, plans are under way for a Joint U.S.-U.S.S.R.

Symposium on High Density Lipoproteins to be held in the Soviet Union. The inclusion of a third U.S.S.R. Lipid Research Clinic in Kiev is receiving serious attention.

Management of Ischemic Heart Disease. Ischemic heart disease (IHD), the subject of joint clinical studies in area 2, is the most common cause of death in the United States and the Soviet Union. It is responsible for chronic illness and disability of many millions of U.S. and Soviet citizens. Improved treatment for IHD is therefore an urgent need in both countries.

The joint U.S.-U.S.S.R. study in the management of ischemic heart disease is an evaluation and comparison of new modes of therapy as opposed to standard medical practice, as well as an assessment of their appropriate roles in modern medical management. In the United States, the surgical technique under study uses a blood vessel graft to bypass a narrowed or occluded segment of a coronary artery. Each year over 80,000 such operations are performed in the United States on patients with varying degrees of chronic disability from angina pectoris (chest pain). The precise indications and the long-term effects of the procedure still remain to be determined. While coronary artery surgery has received considerable acceptance in the United States, the method is much less extensively used in the U.S.S.R. Conversely, some medical approaches in the U.S.S.R. are unfamiliar or unknown to U.S. heart specialists and their coronary patients.

During FY 1978, patient recruitment for the joint study continued in both countries. A U.S. delegation visited the Soviet Union in May 1978, for a Joint U.S.-U.S.S.R. Working Meeting to discuss the ongoing U.S.-U.S.S.R. study of the management of ischemic heart disease, and to discuss plans for future collaborative research and activities. The data from the U.S.S.R. come from patients at the Myasnikov Institute and are part of the ongoing Soviet studies. The patients from the U.S. side come from a national trial involving 15 centers comparing the medical and surgical management of ischemic heart disease. During the meeting, the U.S. and U.S.S.R. scientists agreed that the cooperative study had reached the stage where the data from the two arms of the study should be computerized and put in a form facilitating regular interchanges of information for data analysis. This computerization of joint clinical data is currently in progress at the U.S. Coordinating Center in Seattle. The variables include: detailed coronary angiography, ventriculography, exercise testing with electrocardiography, detailed history, and laboratory data. All of these examinations are carried out according to standardized joint protocols.

During FY 1978, the Proceedings of the First U.S.-U.S.S.R. Joint Symposium on the Management of Ischemic Heart Disease (18 papers) held in Moscow, October 1976, were published in English and will be published in Russian in the Soviet Union in the near future.

Myocardial Metabolism. Myocardial metabolism, or area 3, involves joint basic studies of activities and functions of healthy and

diseased hearts, a subject relating to many areas of cardiovascular research. A fundamental understanding of the structure and function of the heart muscle is crucial to the development of improved methods of prevention and therapy. Specifically, it is important to search for therapies which will enable the heart muscle to survive a heart attack and to develop methods to prevent additional heart muscle damage. The joint U.S.-U.S.S.R. collaboration has emphasized these areas.

The collaboration in area 3 has focused on joint symposia, exchanges of senior scientists, joint laboratory studies by junior scientists for extended periods of time, and a series of joint publications. Three Joint Symposia on Myocardial Metabolism have been held since the beginning of this exchange in 1972. Altogether, 76 scientific reports were presented. The proceedings of all three symposia have been published in English and in Russian, the latest one in FY 1978. Hundreds of scientists and physicians have participated in the exchange during the symposia and visits to laboratories, clinics, and scientific institutions in both countries.

During FY 1978 three senior U.S. scientists and two U.S. fellows visited U.S.S.R. research institutes to engage in joint activities in myocardial metabolism. The U.S.S.R. coordinator for area 3 visited the United States in May 1978, to discuss further plans. A U.S. planning meeting was held in April 1978. Both sides agreed on the following topics for the Fourth U.S.-U.S.S.R. Joint Symposium to be held in the U.S.S.R. in September 1979: hormone action, calcium and membranes, amino acid metabolism, energy metabolism, and myocardial ischemia.

The collaborative efforts have greatly expanded the exchange of information on myocardial metabolism. Each side has agreed to continue joint laboratory investigations in five areas of basic research. Joint presentations of the results of the U.S.-U.S.S.R. studies to date have been made at scientific meetings in the United States and Europe, and a number of joint papers have been published. The potential benefits of this collaboration may be considerable in terms of identifying new approaches to the treatment and prevention of heart disease. This program has already had an impact on the direction of research in both countries, particularly in the area of protecting the heart muscle following a heart attack.

Congenital Heart Disease. Congenital heart disease is a serious illness among children of both countries. It can cause premature death or impair the quality of life from childhood to adulthood.

The objectives of the U.S.-U.S.S.R. collaboration in this area are to explore new methods of diagnosis and postoperative care in order to further reduce mortality from congenital heart disease and improve the surgical treatment of complex heart defects, particularly in very young infants. Each year about 25,000 children in the United States are born with defective hearts. Of the 6,500 of these children who die annually, approximately half are less than 1 year old. Collaborative activities have focused on joint symposia, joint working meetings, and exchange of senior specialists and fellows. Three joint symposia have been held.

Seventy-three reports presented at these symposia have been published in English and in Russian. The *Proceedings of the Third Joint U.S.-U.S.S.R. Symposium on Congenital Heart Disease*, Bethesda, April 14-15, 1977, were published in FY 1978.

A U.S. cardiovascular surgeon visited the Soviet Union during FY 1978 to exchange information with U.S.S.R. surgeons concerning congenital heart disease, to present lectures on topics of current joint interest, and to explore potential topics for the 1980 Fourth Joint Symposium on Congenital Heart Disease to be held in Moscow.

The collaborative activities of U.S. and U.S.S.R. specialists have focused on the etiology and development of pulmonary hypertension; the natural history of ventricular septal defects; the mechanisms of blood coagulation in patients with circulatory hypoxia; and the theoretical aspects and pathophysiology of extracorporeal circulation and deep hypothermia. The joint efforts have produced an expansion of the exchange of information related to the diagnosis, treatment, and follow-up care of patients with congenital heart disease.

Sudden Death. Fifty percent of all deaths from coronary heart disease occur suddenly. The immediate mechanism of sudden death is believed to be a disturbance in the heart's rhythm.

As a result of the joint cooperation in this area a working relationship has been developed between a group of U.S. and Soviet physician scientists. Advanced technology for monitoring of arrhythmias has been exchanged. U.S. scientists have collaborated with Soviet scientists in organizing a monitoring study for identifying subjects at high risk for sudden death in the Sokolniki area of Moscow. The Soviet side has shared data on coronary heart disease patients who underwent ambulatory monitoring, and the United States has provided data on Multiple Risk Factor Intervention Trial subjects who have been screened for cardiac arrhythmias.

The U.S.S.R. side has identified a large group of patients with complex arrhythmias who are at high risk of sudden death. This has led to a cooperative study in Moscow, using an acute antiarrhythmic drug testing protocol developed in the United States. During FY 1978 a U.S. exchange scientist spent 3 months in the U.S.S.R. cooperating in this study. The work dealt with an investigation of two new antiarrhythmic drugs: ethmozin, developed in the U.S.S.R., and a second agent, Mexiletine.

A Joint Symposium on Sudden Death was held in Yalta in October 1977. The proceedings of the symposium were published in FY 1978 in English and in Russian. Both sides have agreed to intensify the exchange of information by preparing annotated bibliographies of the most important recent papers on sudden death in their respective countries and through the formation of U.S. and U.S.S.R. editorial groups to prepare articles for joint publication in U.S. and U.S.S.R. journals. As a result the exchange of information was increased significantly during FY 1978.

Six areas have been designated for continued exchanges of specialists. A U.S.S.R. working group will visit the United States in the fall of 1978 to assist in planning the Joint Working Symposium on Sudden Death to be held in the United States in 1979. The delegation will also visit U.S. laboratories.

The collaboration in area 5 should help bring into focus current activities and possible future discoveries concerning control of sudden death and the arrhythmias that may lead to sudden death. There is mutual recognition that effective control of sudden death will bring about significant reductions in coronary heart disease death rates in both countries.

Blood Transfusion, Blood Components, and Prevention of Hepatitis with Particular Reference to Cardiovascular Surgery. Blood resources, a nation's supply of blood and blood products, are critical to the health of its citizens. High quality blood management is a necessary adjunct to successful cardiovascular surgery as well as other forms of therapy. Prevention of hepatitis in transferring blood from donors to recipients is a goal common to both the United States and U.S.S.R.

The past two decades have witnessed rapid advances in blood management. However, this progress has been matched by steady increases in demand caused by parallel advances in medical sciences and technology. This, in turn, necessitates continuous development of new approaches to upgrade blood therapy.

The U.S.-U.S.S.R. cooperation has focused primarily on joint working meetings, exchanges of scientists for joint laboratory studies, and exchange of information at one symposium. Information has been exchanged on the U.S. blood transfusion system, blood service in the U.S.S.R., new methods of blood preservation used in the two countries, utilization of blood components, blood transfusion technology, problems of hepatitis, effects of massive blood transfusions, use of blood in cardiovascular surgery, and problems related to the use of blood in heart bypass systems. Collaborative activities focus on two areas: prevention of hepatitis in blood transfusion, particularly in cardiovascular surgery; and the use of whole blood, blood components and derivatives, emphasis on cardiovascular surgery.

Joint studies on hepatitis were initiated in FY 1978. Altogether, about 1,000 serum samples from each country were exchanged. These cooperative investigations on the frequency of distribution of hepatitis B markers in sera of donors will provide information on the frequency and etiology of post-transfusion hepatitis and particularly non-A, non-B hepatitis in cardiovascular surgery patients for clinical investigation of immune globulin of hepatitis B, and for the development and evaluation of vaccines against viral hepatitis B.

Two U.S. fellows visited the U.S.S.R. during FY 1978 for joint laboratory studies and lectures on topics of joint interest in blood transfusion, blood resources, and hepatitis. The Soviet side shared information on a technique for significantly increasing the yield of antihemophilic factor from blood. It is anticipated that application of this

technique in the United States will result in considerable savings in blood resources and costs. Two U.S.S.R. scientists visited the United States under the individual scientist exchange for discussions in area 6. A U.S. delegation visited the U.S.S.R. in September 1978, for a Joint U.S.-U.S.S.R. working meeting to present lectures, to develop further joint plans, and to visit U.S.S.R. laboratories collaborating in the exchange. The *Proceedings of the First U.S.-U.S.S.R. Symposium on Blood Transfusion* were published during FY 1978.

The investigations carried out in area 6 have emphasized the need to restrict the use of whole blood during cardiovascular surgery. There are now new possibilities to supplement whole blood with blood components and substitutes. It is hoped that the joint activities will lead to new approaches to blood transfusion methodology in cardiovascular surgery.

Hypertension Etiology, Treatment and Prevention. Hypertension is one of the major health problems in the world, both in terms of its prevalence and its impact. About 35 million Americans (1 in 6) have definite high blood pressure (160/95 or higher) and are at significant risk for future cardiovascular, cerebrovascular, and renal disease. The prevalence of high blood pressure increases strikingly with age. It is twice as prevalent, and twice as malevolent in black Americans. Another 25 million Americans have so-called "borderline" high blood pressure (with pressures between 140/90 and 160/95) and probably warrant regular medical surveillance. The hypertension problem in the U.S.S.R. is also a serious one. As a result, the U.S.-U.S.S.R. joint committee decided to add Hypertension Etiology, Treatment, and Prevention as a new area of joint collaborative activities under the cardiovascular exchange in FY 1978.

Two senior U.S.S.R. scientists visited the United States during FY 1978 to develop joint plans in this area, participate in meetings on hypertension, and visit scientific institutions and laboratories. A Joint U.S.-U.S.S.R. Symposium on Hypertension was held in June 1978 in Sochi. The aim of the symposium was to exchange scientific information on fundamental, clinical, and epidemiological aspects of hypertension in both countries. Both sides presented overviews of the hypertension studies in each country; approaches to methodology; experimental models of neural and humoral control of blood pressure; hemodynamic factors in hypertension; malignant forms of arterial hypertension; and epidemiology of hypertension.

Interesting new hypertension findings from the Joint U.S.-U.S.S.R. Lipid Research Clinic Studies were reported. As a result of the use of common, highly standardized methods in epidemiological surveys carried out in the Joint U.S.-U.S.S.R. LRC program, it is possible to compare the prevalence and treatment status of high blood pressure in men sampled from Moscow, Leningrad, and nine U.S. communities. The preliminary data show that, in the populations studied, U.S.S.R. men aged 40-59 have higher levels of blood pressure than U.S. men of comparable age. The prevalence of high blood pressure is two to three times

greater in Soviet than U.S. white men. Also, the prevalence of hypertension is higher in hyperlipidemic men than in random sample examinees in both countries. The U.S. delegation to the symposium also visited Soviet research institutes and work settings to discuss joint programs in hypertension.

The *Proceedings of the Joint Hypertension Symposium* will be published in English and in Russian. The following joint activities were agreed upon for the future: Cooperation in Basic and Clinical Research; Cooperation in Research on Hypertension Control; and a Second Joint Meeting on Hypertension in the U.S.A. in May 1979.

Artificial Heart Research and Development. In June 1974, after several years of exploratory discussions, both governments signed a 3-year agreement designating the field of artificial heart research and development as a new area of cooperation. Mutual interest in this area stems from the recognition that present and foreseeable techniques of surgical and pharmacological management of acute and chronic heart failure and shock still leave a substantial fraction of patients with compromised or fatally impaired heart function. By supportive mechanical devices, it is possible to assume some of the pumping function of the heart and to relieve its workload. Presently such techniques are applicable for brief periods in man and have been employed for longer periods in experimental animals. Studies of patients in the United States have shown a definite reduction in the workload of the heart following a heart attack when the heart is assisted during recovery by means of a mechanical pumping device.

The U.S.-U.S.S.R. Agreement in Artificial Heart Research and Development was renewed in 1977 for a period of 5 years together with the overall health exchange agreement. The agreement calls for implementation principally by exchange of scientific and technical information; organization of joint conferences; workshops and meetings of experts; exchange of specialists and delegations; preparation of joint publications and technical manuals; and familiarization with and exchange of technical aids and equipment.

In implementing the joint collaboration, an immediate problem was the disposition of rights on any patents resulting from collaborative work in this area of advanced technology. As a result of joint efforts, a bilateral agreement setting forth guidelines for disposition of intellectual property questions was signed by both sides in 1975 in Russian and in English.

During the past several years the joint collaboration has emphasized joint working meetings, exchanges of protocols, exchanges and testing of devices from each country, and exchanges of working teams and individual scientists. Six artificial hearts and one drive system from each side were exchanged during the first 3 years of the exchange. Preparations are in progress for the exchange of a vacuum forming device and biomaterials from the United States and a circulatory device control system from the Soviet Union.

During FY 1978 a delegation from the Soviet Union visited the United States for a joint U.S.-U.S.S.R. working meeting in Houston to discuss progress and to jointly draft plans for future activities. The delegation also visited a number of U.S. centers with ongoing research in circulatory device development. The agenda for the joint meeting included presentations on artificial hearts and several discussions of energy conversion systems for circulatory devices and circulatory device control systems. At the conclusion of the meeting, both sides agreed on continued exchanges of scientists for work in each others' laboratories, exchanges of individual scientists and delegations to further develop joint activities, and publication of joint articles on U.S.-U.S.S.R. activities and exchanges completed to date. The U.S. and U.S.S.R. scientists also agreed to hold a joint working meeting and a joint symposium in the U.S.S.R. in the fall of 1979 to review progress and to develop further plans. A joint publication on the exchange to date is in preparation.

Two U.S.S.R. exchange fellows visited U.S. laboratories during FY 1978 for joint studies in artificial heart research and development; reciprocal exchanges of U.S. fellows are planned.

Cooperation With Israel

The Jerusalem Lipid Research Clinic is the latest addition to the NHLBI International Lipid Research Clinics Program. It was established by the Institute in 1975. During FY 1978 progress continued in the prevalence study of dyslipidemia and its natural history in the Jewish population of Jerusalem. The study screens 17-year-old boys and girls when they report for preinduction physicals for the Army.

The attraction for performing this study in Jerusalem is the multiethnic character of the population. No other place in the world currently provides such an opportunity for conducting a multinational study in a microcosm. The ethnic groups represented in the study differ significantly with respect to heart disease rates, dietary patterns, education, and socioeconomic status. The current study will be completed in 1979, with an additional 2 years required for followup analysis of the data. The target is to screen about 15,000 individuals by the end of 1979, approximately 7,500 youngsters and 7,500 adults. About 8,000 youngsters and 5,300 adults had been screened as of July 1978.

While the study is still ongoing, sufficient numbers of individuals have been screened to allow preliminary analyses of the data. Important findings already have been noted on differences in lipid distribution in the population, dietary differences in fat intake, and comparative data on the national diets of the United States and Israel.

The results of international investigations such as those conducted in the U.S. and Jerusalem LRC's are of great importance to medical science. If these studies establish that lowering blood cholesterol indeed decreases the risk of heart attacks, many lives will be saved. However, if the studies determine that lowering cholesterol does not prevent heart

attacks, our society can be spared the expense and social hardship of cholesterol-lowering diets and drugs. In either case, the medical information originating from the LRC international investigations will profoundly affect millions of lives in this and future generations.

Cooperation With the Federal Republic of Germany

During FY 1978 the Institute continued its cooperation with scientists in the Federal Republic of Germany (F.R.G.) under the Agreement on Cooperation in the Fields of Biomedical Research and Technology signed in September 1976 by the U.S. Assistant Secretary for Health and the Minister of Research of the F.R.G.

The German side expressed a special interest in collaboration in cardiovascular disease, and a series of planning meetings were held during FY 1978 to develop plans for joint activities in this area. As a result, collaborative activities were initiated in two areas, arteriosclerosis and hypertension. Projects to be considered will fall within the spectrum of etiology, pathogenesis, and prevention. Both sides exchanged extensive information on ongoing projects in arteriosclerosis and hypertension, and the German side developed proposals for potential joint collaboration. In many cases collaborative activities were already under way with U.S. laboratories. Some of the proposals dealt with the need for developing standardized assays for biologically active compounds such as the reninangiotensin system and plasma lipoproteins and apoproteins. It was felt that development of such common methodologies and their adoption in the United States and F.R.G. would allow accurate comparisons of data by different laboratories and would allow the development of a more comprehensive data base than would otherwise be possible. Since the German data base is tied to the rest of Europe, adoption of such methodologies would make it possible to obtain comparative epidemiological data not only for the U.S. and Germany but also for other countries in Europe.

A Joint U.S.-F.R.G. Workshop on Hypertension and Arteriosclerosis was held in Heidelberg in August 1978 to review the proposals for potential joint activities and to develop plans for joint or complementary activities. The emphasis was on linking ongoing projects in both countries and on the exchange of scientists.

At the conclusion of the workshop, a Joint Summary of Discussion was signed by both sides outlining plans for further activities. It was agreed that the U.S.-F.R.G. agreement provided an important opportunity for advances in biomedical research and health care which might benefit the peoples of both countries. The proposals developed by the German side were most valuable in the discussions. The two sides agreed that the proposed U.S.-F.R.G. activities in prevention, education, and control will necessitate continued basic biomedical research in both countries. Highest priority was given to the exchange of biomedical scientists. Priority was recommended in establishing German studies

(data sites) on cardiovascular disease, morbidity and mortality, and risk factors similar to those developed from studies in the United States. The German side expressed an interest in having U.S. scientists work with them in the planning and development of such studies. Also, the German side accepted the U.S. invitation for an F.R.G. delegation to attend the National Heart, Lung, and Blood Institute Conference on the Decline in Coronary Heart Disease Mortality to be held in Bethesda in October 1978.

The U.S. delegation's itinerary included visits to laboratories and clinics. In addition, the NHLBI Director was invited to Bonn to meet with representatives of the three ministries participating in the U.S.-F.R.G. exchange in the cardiovascular area. The purpose of these meetings was to discuss policy and administrative questions concerning future cardiovascular exchanges. The German side is particularly interested in duplicating the U.S. experience in the decline of cardiovascular disease. The Institute is looking forward to collaborating with the F.R.G. side to further delineate the role of various risk factors thought to be responsible for the positive change in cardiovascular disease in our own country. The two sides have agreed to develop a data base of ongoing investigations, especially as they relate to programs of intervention on risk factors. A meeting of scientists from both countries will be held in the second part of 1979 to share data and to develop specific plans for joint studies.

Cooperation With the Republic of Italy

During FY 1978 the Institute initiated collaboration with Italy under the Memorandum of Understanding between the Department of Health, Education, and Welfare of the U.S. and the Ministry of Health of the Italian Republic for Cooperation in the Field of Health and Medicine, signed in November 1977. A series of joint planning meetings were held in accordance with a joint implementation plan agreed upon in March 1978 for collaboration in the prevention of heart disease. The plan calls for three types of initial activities: exchange of information on pertinent U.S. and Italian studies; translation of key U.S. and Italian documents into Italian and English, respectively; and a Joint U.S.-Italian Workshop on Measurement and Control of Cardiovascular Risk Factors and visits to Italian scientific institutions and laboratories. The purpose of the workshop, held in December 1978 in Rome, will be to exchange, review, evaluate, and compare U.S. and Italian information on mortality, morbidity, prevalence, and incidence data on cardiovascular diseases; nutritional data; relationships and trends between major risk factors and cardiovascular disease; and methodologies for measurement and control of risk factors. Three cardiovascular risk factors will be highlighted: hyperlipidemia-nutrition, hypertension, and smoking.

Cooperation With Poland

The Minister of Health for Poland and a delegation of health experts visited the NHLBI in September 1977 to discuss opportunities for joint collaboration in heart and vascular diseases, lung diseases, blood diseases, and blood resources. The Minister extended an invitation to the Director, NHLBI, to visit Polish research institutes in the spring of 1978. The visit has been postponed and will be rescheduled in the future.

A Joint U.S.-Polish Symposium on Cardiovascular Diseases will be held in Bethesda in November 1978 at the request of the Polish Ministry of Health in recognition of U.S.-Polish "Medical Week." The meeting will deal with epidemiology of cardiovascular diseases, overview of major areas of research emphasis, specific discussions of research in hypertension and arteriosclerosis, the transfer of technology in cardiovascular diseases, and cardiological care and postgraduate education.

As part of the ongoing U.S.-Poland cooperation in biomedical research which provides counterpart P.L. 480 currencies, progress continued on the Research Agreement for the Polish component of the ongoing European Collaborative Trial in Multifactorial Prevention of Coronary Heart Disease, signed in November 1976. During FY 1978, Institute staff visited Poland to review and discuss the data with their Polish colleagues. In both Warsaw and Cracow factories participating in the trial, cooperation in the screening program was excellent with an average participation in all factories of about 88 percent. Nearly 9,000 screening examinations were completed (the goal is 10,000), 8,042 in factories designated as "intervention" factories and 713 (a targeted 10 percent of the factory employees) in the "control" factories. Risk factors targeted for intervention include hypercholesterolemia, overweight, hypertension, smoking, and lack of physical activity. Preliminary data show blood pressure and cholesterol values to be higher in Warsaw than in Cracow. Prevalence of cigarette smoking is much higher than in the U.S. study: 62 percent current smokers (Warsaw) vs. 37 percent (U.S.).

Cooperation With Yugoslavia

An agreement between the Government of the United States and the Government of Yugoslavia was signed in May 1973 to encourage research between the two countries on projects of mutual interest. With the P.L. 480 funds provided under this agreement, NHLBI scientists have collaborated with Yugoslav scientists on two projects, one dealing with Epidemiology of Cardiovascular Diseases, and the second with Epidemiology of Respiratory Diseases. This international collaboration has yielded a number of interesting new findings and gained the attention of the international medical community. Joint review and analysis of the data continued in FY 1978.

More than 11,000 Yugoslav men are included in the long-range followup for cardiovascular risk factors. The coronary heart disease (CHD) incidence in Yugoslav men appears to be extraordinarily low. It is about one-fourth the incidence in the U.S. Framingham study. By comparison, the CHD incidence among men in the Framingham study is typical of that found in a number of comparable prospective studies in the United States. The Framingham incidence, in turn, is double that in Puerto Rican men and Japanese men living in Honolulu. Some of the results of the U.S.-Yugoslav collaborative study will be reported at the October 1978 International Symposium on Essential Hypertension to be held in Yugoslavia at the initiative of the principal investigator on the U.S.-Yugoslavian project. Repeat measurements of blood pressures taken 7 years apart show increases in both diastolic and systolic pressures and increases in the prevalence of high blood pressure over this period. The increases are larger in rural than in urban areas. It will be of interest to see whether these trends will continue as the impact of Westernization continues.

During FY 1978, work also continued on the analysis of data from the large respiratory project conducted in Yugoslavia with P.L. 480 funds in which about 3,000 individuals have been phenotyped for anti-trypsin genes. The basis for this extensive study is the finding that a genetic defect resulting in a deficiency of the enzyme alpha-1-anti-trypsin has been identified as a factor in the development of a severe form of familial emphysema which attacks young adults. Unexpectedly, during this study, a new antitrypsin gene was discovered and first identified in Belgrade and St. Louis with subsequent verification by other laboratories. This study was completed in FY 1978 but analysis and publication of results is likely to continue in the future.

Cooperation With Great Britain

Scientists from the NHLBI Division of Intramural Research continued their cooperation with scientists from Great Britain in the development of a computer-based chemical information system (CIS). While the management for the CIS continued to be located in NHLBI, funding during FY 1978 was largely drawn from the NIH management fund. During FY 1978 the development of the CIS progressed faster than at any time in the past. The system includes analytical programs to accomplish iterative analysis of complex NMR spectra, or general curve fitting and linear regression analysis. The data base for the system was assembled by the joint efforts of the National Institutes of Health, the Mass Spectrometry Data Center (within the Department of Industry of the British Government), and the Environmental Protection Agency, with participation from several other U.S. Government agencies as well as nongovernment U.S. units. This valuable information system is being made available to scientists in North America and in Europe by means of an international teleprocessing network.

The following countries currently cooperate in the further development of CIS: Finland, France, Germany, Holland, Hungary, Japan, Poland, Sweden, Switzerland, U.S.S.R., and Yugoslavia.

Cooperation With Other Countries

The National Heart, Lung, and Blood Institute participates in the work of the NIH Coordinating Group for the U.S.-Egyptian Joint Subcommittee on Biomedical Research. The Egyptian side has submitted proposals in several areas falling within the Institute's mission and an Egyptian scientist visited the U.S. in FY 1978 to develop a joint research proposal. The Institute continued informal contacts with Japan in the cardiovascular, lung, and blood resources areas. The director, Division of Lung Diseases, NHLBI, is the NIH representative on the Panel on Lung Physiology and Technology of the U.S.-Japan Natural Resources Agreement. NHLBI staff members were invited to Japan in the fall of 1978 to participate in joint meetings on hypertension and meetings of the U.S.-Japanese Panel on Malnutrition. The Institute has indicated interest in participating in the proposed U.S.-Japan umbrella agreement. The NHLBI continued to assist in the analysis of the British-Norwegian Migrant Study. The Institute also collaborates in the U.S.-France Agreement for Scientific and Technological Cooperation in research on lung diseases. Proposals are pending for Institute participation in collaborative activities with several additional countries.

Coordination With International Organizations

During FY 1978 the Institute continued to collaborate with the WHO. The Director, NHLBI, was appointed advisor to WHO in long-range planning of programs in cardiovascular diseases. Institute staff collaborated with the International Society and Federation of Cardiology and WHO in developing programs for World Health Day, April 7, 1978, which was devoted to hypertension. NHLBI staff participated in WHO planning workshops on: hypertension; links between cardiovascular diseases and other chronic diseases; long-term effects of coronary bypass surgery; and the WHO Cooperative Study of Present Research on Atherosclerosis and Hypertension Precursors in the World. The Institute also continued to contribute to the WHO Mild Hypertension Liaison Committee.

International Visitors and Meetings

During FY 1978 the Institute received many international scientists for joint work in the laboratories of the Division of Intramural

Research, NHLBI. These scientists came from Australia, Brazil, Cameroon, Canada, Great Britain, India, Israel, Italy, Japan, Mexico, Peru, South Africa, and Taiwan. Many international scientists participated in the Fourth U.S. National Conference on High Blood Pressure Control.

The Institute staff attended a number of international scientific meetings during FY 1978, actively participating in these meetings as speakers, panelists, and chairmen. Examples of important meetings are: World Conference of International Union Against Tuberculosis and Respiratory Diseases; World Congress of Cardiology; International Symposium on Diet and Atherosclerosis in Pediatrics; International Congress of Pediatrics; Latin American Congress of Pathology; International Society of Hypertension; International Congress of Nephrology; International Congress of Pharmacology; International Biophysics Congress; Congress of the International Academy of Pathology; International Symposium on Prophylactic Approach to Hypertensive Disease; and the International Society of Hematology and International Society of Blood Transfusion meetings.

An Institute staff member visited Africa at the invitation of the College of Medicine in Nairobi, Kenya, and brought back reports on the many illnesses and deaths preventable in terms of U.S. medical practices.

Institute Trends in International Activities and Proposed New Directions

International cooperation in health is in the interest of the citizens of the United States as well as those of other countries. It provides an important and unique resource for expanding and sharing America's own resources for dealing with problems in health research and health care. Through such cooperation the talents, insights, and experiences of many nations can be brought to bear on the analysis and planning of U.S. national programs as well as priority setting for the future. By making fuller use of the international resources in science and medicine, the Institute hopes to create an even stronger base for the future development of the National Heart, Blood Vessel, Lung, and Blood Program mandated by the President and the Congress and thereby improve and cut the costs of health care for U.S. citizens.

In recent years, the United States has increasingly encouraged international cooperation in biomedical research by entering into bilateral health exchange agreements and by authorizing the expenditure of funds for international activities. In a statement emphasizing the importance of "International Health Programs" the President's Biomedical Research Panel stated, "There is now a steadily growing, international community of biomedical science in which the free exchange and the setting up of collaborative scientific projects represent not only practical steps toward more productive research but also perhaps, an encouraging manifestation of the comity of nations."

By bringing the total international experience in biomedical research to bear on specific national programs and by developing joint programs with other nations in selected areas of mutual interest it should become possible for the United States as well as other countries to realize significant savings in cost, resources, and time to bring about mutually desirable health outcomes. For instance, the development of standardized international methodologies will help decrease the need for duplicating large-scale studies done in other countries.

Since the passage of the National Heart, Blood Vessel, Lung, and Blood Act in 1972, the international activities of the National Heart, Lung, and Blood Institute have expanded significantly reflecting the increasing encouragement by the Department of Health, Education, and Welfare and the Department of State to expand international cooperation in biomedical research. There has also been a parallel increased interest on the part of foreign governments to establish formal international agreements for collaborative programs in the areas falling within the mission of the national program.

The world problems in cardiovascular, lung, and blood diseases and blood resources are interrelated, and it is important that a global perspective be sought in constructing means for finding solutions to these problems. Nationally and internationally there is a new preoccupation with the interrelationships between economic considerations, health status, and health outcomes. Comparisons are being made between the costs and resources required to bring about various levels of improvement in health status by different means, whether scientific, economic, or social in nature and between various systems of delivery for these improvements, and the Institute is aware of these concerns.

Unless preventive measures are taken, past experience in the industrialized nations strongly indicates that the socioeconomic advances desired by developing nations as well as developing segments of our own society will be accompanied by a costly epidemic rise in cardiovascular and other diseases similar to that now experienced by most industrialized nations. This can be prevented by international collaboration and sharing of knowledge and experiences in health research.

A number of specific opportunities for continuing and new international collaborative efforts were identified during FY 1978. These will be pursued in accordance with national priorities and as resources become available for international activities. It is planned that these programs be developed in an orderly manner (i) by following through on specific leads identified by U.S. scientists, (ii) by following up on indications of interest from scientists and government officials from other nations with respect to unique patient populations or unique resources that could be explored jointly with U.S. investigators, and (iii) by exchange visits and joint programs in areas of common need and mutual interest.

Specifically, the Institute plans to continue ongoing bilateral exchange programs and collaboration with the World Health Organiza-

tion in the planning and development of long-range international programs in cardiovascular disease. Plans are in progress for a joint U.S.-P.R.C. scientific meeting on "Cardiovascular Diseases" to be held in November 1978, at the National Heart, Lung, and Blood Institute at the request of a delegation of cardiologists from the People's Republic of China. A Joint U.S.-Polish Symposium on "Cardiovascular Diseases" is also scheduled for November 1978, at the request of the Polish Ministry of Health in recognition of U.S.-Polish Medical Week. During FY 1978, the Institute also had a number of visits from representatives of Eastern European countries interested in collaboration and we expect these contacts and exchanges to continue in the future.

The HEW trend during the past year has been to focus attention on the increasing need for industrialized nations such as the United States to help countries which are less economically advantaged in their health research development. Some of the inquiries received have been close to home as exemplified by the efforts to focus attention on research programs along the U.S.-Mexico border. Others have dealt with developing countries in Asia, Africa and Latin America. The Institute is interested in cooperating in these efforts by the U.S. Government to share experience and develop joint research with developing countries. Specific opportunities for collaboration have been identified. The extent to which the Institute can implement these plans will depend upon the availability of U.S. funds for travel and program operation of such activities.

The National Heart, Lung, and Blood Institute plans to continue to develop its international role within the policies and budgetary constraints set by the President and the Congress. We expect this development to include formal as well as informal arrangements in accordance with national priorities and new international leads and opportunities for scientific exchange.

National Institute on Aging

The broad mandate of the National Institute on Aging (NIA) for a multidisciplinary approach to the study of aging is reflected in the Institute's international activities. Foreign visitors to NIA represent a variety of disciplines and interests. NIA cooperated with the Swedish Embassy in planning miniconferences in six cities whereby Swedish gerontologists discussed their programs and activities in aging. A conference on senile dementia brought together American and foreign experts to discuss and exchange information on the study of this problem.

In the Spring of 1978, Dr. Milo D. Leavitt, former Director of Fogarty International Center and currently the NIA Director's special

assistant for Medical Program Development and Evaluation, spent 6 weeks visiting 8 of the 10 British medical schools with chairs in geriatric medicine and studying the educational, research, and service aspects of geriatric medicine in that country. His purpose was to determine training opportunities that might be developed via a fellowship program in geriatric medicine for postdoctoral U.S. physicians.

The NIA nominated Sir Ferguson Anderson, a well-known British geriatrician, to be a Fogarty International Scholar. He plans to arrive in September 1979, to participate in activities to further the development of geriatric training in the United States.

P.L. 93-296, The Research on Aging Act of 1974, created the NIA to promote research into the biological, medical, psychological, social, and behavioral aspects of aging.

Aging research spans a wide range of disciplines from cellular biology to the social sciences, i.e., studies of the aging processes, social and psychological factors associated with aging, and alleviation of problems of old age. Such studies are conducted at NIA's laboratories and at other research institutions through grants from NIA.

The mission of NIA is to study the aging process and factors associated with aging, and the alleviation of problems of aging. This mission differs from those of Institutes charged with research related to specific diseases. The NIA, therefore, cooperates with other Institutes in studies of diseases associated with aging. With the growing aged population in the United States and in the world, all nations are aware of the need for research in aging.

In cooperation with FIC and WHO, NIA, in November 1977, convened the directors of national institutes in other countries with programs in the field of aging to discuss geriatric teaching, training, research, and services in their countries. A followup conference of these directors was held in Toyko, Japan, August 1978, in connection with the International Congress of Gerontology.

A roundtable discussion was held with the U.S. Senate Special Committee on Aging and with Mrs. Carter at the White House during the November 1977 conference.

In November 1978, a delegation from the Ministry of Health, Budapest, Hungary, met with staff to explore research opportunities of mutual interest and the possibility of future collaboration between the United States and Hungary.

Both WHO and the U.N. are addressing the problems of the aged. The U.N. has passed a resolution for a World Assembly on Aging in 1982 at which NIA expects to play a major role. In addition to such conferences, the exchange of scholars and information is vital to the dissemination of knowledge.

NIA will continue to provide assistance and information and play a consultative role in research on aging, particularly to developing nations.

National Institute of Allergy and Infectious Diseases

Introduction

Since health problems of the tropical and developing countries are still largely those of infectious diseases, much of the biomedical research supported by the National Institute of Allergy and Infectious Diseases (NIAID) has strong international application. In addition to the usual tropical and parasitic diseases that commonly come to mind, such as malaria, schistosomiasis, cholera, and leprosy, the developing world is also plagued by diseases much more familiar to us in the temperate world such as hepatitis, the virus respiratory and enteric diseases, sexually transmitted diseases, tuberculosis, and various allergies. The infectious diseases are often more prevalent and more severe in the tropics and developing countries as a result of poor sanitation, inadequate education about how diseases are spread and prevented, and the common occurrence of malnutrition, all factors which combine to intensify the impact of these problems. The objectives of NIAID-supported research activities of international interest are the same as those for its domestic interests, namely, to supply new information on disease mechanisms that is requested to develop improved methods for diagnosis, treatment, and prevention.

The work of NIAID takes place in laboratories at the NIH as well as in those at academic institutions in the United States supported by grants or contracts from the NIAID. A few grants are made to investigators in foreign institutions, but these must compete for funding successfully with the large number of high quality domestic research grant applications. Several other mechanisms are available for support of research in tropical medicine: grants to U.S. institutions with a close link to a foreign institution (ICMR Program), and collaborative research funded in certain countries with U.S.-owned foreign currency (P.L. 480). Additionally, there are bilateral medical science research programs with several countries, such as the U.S.-Japan Cooperative Medical Science Program. Table 1 lists the main categories of NIAID programs in tropical medicine and their approximate budgets in FY 1978.

While much of the research on infectious and allergic diseases supported by NIAID is generally applicable to those same categories of disease throughout the world, the remainder of this report will emphasize primarily the research work supported by the NIAID that relates to those special health problems of the tropical and developing countries which have minimal direct impact in the United States.

Extramural Program of Grants and Contracts

Of the total portfolio of NIAID extramural grants and contracts, 212 could be considered in the areas of tropical medicine since they

**Table 1. Main Categories of NIAID Programs in
Tropical Medicine and International Health — FY 1978**

Extramural Program*

(Parasitology, medical entomology,
leprosy, cholera, arbovirology)

Grants and Contracts	\$14,633,951	(212)
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Intramural Program

LPD (59 personnel)	\$ 3,158,000
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RML 1/10 (13 personnel)	<u>402,000</u>
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Total Tropical Medicine	\$18,193,951
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Foreign Competing Grants	<u>\$ 810,452</u>	(26)
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Total International	\$19,004,403
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*The U.S.-Japan Program grants and contracts are included but this does not include the ICMR's.

dealt with research in parasitology, medical entomology, cholera, and arbovirology. In addition, 26 competing grants were made to investigators in foreign countries, but only 2 or 3 of these were in the field of tropical medicine or parasitology. These 212 domestic and 26 foreign grants or contracts include grants and contracts for the U.S.-Japan Program, but not for the International Centers for Medical Research (ICMR's); however, these programs are described separately. The legislative authority for NIAID grants and contracts stems from the Public Health Service Act of 1955, Public Law 81-692, Title III, Part A, Section 301, and Title IV, Part D, Section 431.

The objectives of the program are the development of new knowledge applicable to diagnosis, prevention, and treatment of the relevant tropical and parasitic diseases.

During FY 1978, total expenditures for the NIAID Tropical Medicine Extramural Program of 212 grants referred to above was nearly \$14 million. This could be broken down to 148 grants for about \$9.5 million in parasitology and medical entomology, 15 grants of \$1.4 million for work on leprosy and cholera, and 19 grants in arbovirology for \$1.9 million dollars. Another \$1 million is allotted to 20 fellowship and training grants. These data are tabulated in table 2.

Table 2. NIAID-EP Tropical Medicine Program — FY 1978

212 Grants ¹	— Parasitology and Medical Entomology	
	Research	\$ 9,578,770 (148)
	Training	562,393 (9)
	Fellowships	167,816 (13)
	Research careers	<u>272,798 (8)</u>
	Subtotal	\$10,581,957 (178)
	— Leprosy	\$ 577,025 (6)
	— Cholera	\$ 830,948 (9)
	— Arbovirology	<u>\$ 1,900,309 (19)</u>
	Total	\$13,890,239 (212)
	¹ Does not include 4 ICMR's for \$2,100,000 (est.)	
10 Contracts	— (U.S.-Japan Program only)	
	— Schistosomiasis	\$ 118,080 (1)
	— Filariasis	\$ 136,454 (3)
	— Leprosy	\$ 230,485 (3)
	— Cholera	\$ 258,693 (3)
	— Arbovirology	<u>\$ 0 (0)</u>
		\$ 743,712 (10)

Some of the research findings reported during FY 1978 from the Extramural Program are summarized below. For purposes of brevity they cover only the diseases given emphasis by the WHO/TDR program on international health, including leprosy.

Malaria

The NIAID supports 12 individual research grants involving malaria. One of the grantees has successfully separated sporozoites of several *Plasmodium* species from mosquito debris and microbial contents by passing mosquito material through a DEAE-cellulose column. This simple technique has made possible not only the elimination of most of the contaminants, but the recovery of large numbers of viable sporozoites that have retained their infectivity, immunogenicity, and capacity to react with known antisera. This technique will be utilized in a long-range study of active and passive immunity against malaria. Another grantee has been able to develop a simple, effective means for differentiating parasite and host cell membranes by staining with cationized ferritin

followed by electron microscopic observation. He showed that the surface membranes of the parasite differ from one another and from the plasma membrane of the erythrocyte. Employment of these techniques should enable investigators to assess the purity of isolated parasite preparations as well as aiding in identification of various membrane systems found in the parasite after subcellular fractionation.

Schistosomiasis

The NIAID supports 25 individual research grants relating to schistosomiasis, as well as 2 fellowships, 3 training grants, and 1 program project. A contract to supply investigators with mammals of vectors infected with several strains of the three human species of schistosomes has continued to stimulate research on a broad scale.

In a grant-supported field study of a population in an endemic area of schistosomiasis in the Philippines, several commonly used diagnostic tests were compared. This study showed that the filter paper circumoral precipitin test is neither reliable nor sensitive despite its popularity and mass application. Another grantee has isolated a potent inhibitor of activated Hageman factor in *S. mansoni*. This inhibitor may explain the ability of adult worms to avoid contact activation of the coagulation system in situ in the mesenteric veins. In a study of snail-trematode interactions, with the ultimate goal of finding clues leading to the development of schistosome biocontrol, a third grantee has shown that natural resistance in snails may be highly specific, involving not only distinct species but parasite strain differences as well.

Filariasis

The NIAID supports 10 individual research grants relating to filariasis. The Institute also funds a supply contract to provide investigators throughout the United States with animals and vectors infected with various species of filarids. This contract, as in the case of the schistosomiasis supply contract, supplies researchers who would otherwise be unable to obtain or maintain parasite life cycles but whose disciplines (immunology, pharmacology, biochemistry, etc.) must be brought to bear on the complex problems involved in the overall control of these tropical diseases. Two smaller contracts have as their objective the development of techniques for the cryopreservation of filarid material. Such techniques are essential in the shipment of samples of human filarial parasites from field collection sites to base laboratories, particularly those in the United States.

One NIAID grantee has shown that in the cat model of elephantiasis a concurrent infection with beta hemolytic streptococci results in greatly increased pathology. This is the first experimental study carried out in an animal model resembling human elephantiasis.

Another grantee has demonstrated that a small particle size formulation of a new antifilarial drug (CGP4540) has a high chemotherapeutic activity when administered in a single oral dose to gerbils infected with the filarial worm, *Brugia pahangi*. This formulation has also been found to be highly effective against schistosomes. To date no toxic effects have been noted.

Trypanosomiasis

Individual NIAID research grants relating to trypanosomiasis have been made to 13 investigators. In addition, the Institute supports one training grant. Research under these grants is concerned with trypanosome pathogenicity, metabolism, chemotherapy, and immunology. In a comparative study of the antigenic differences between pathogenic and nonpathogenic trypanosomes, one of the grantees has shown that the reproduction-inhibiting antibody, albastin, produced by the nonpathogenic *T. lewisi* is an avid IgG antibody. The relevance of this finding is that it is now technically possible to isolate, purify, and characterize its antigen. Such knowledge should provide insight into how parasite reproduction is controlled by the host.

A second grantee is growing the causative agent of African trypanosomiasis in vitro. Growing *T. rhodesiense* in vitro in hamster lung is making possible long, in-depth, sophisticated biochemical studies. The parasites have been maintained for over 3 months with retention of infectivity to rats and mice.

Leishmaniasis

The NIAID supports 6 individual research grants on leishmaniasis. One of these grantees, located at the World Health Organization, has been studying normal mouse peritoneal macrophages that have been infected in vivo with *Leishmania enriettii*. When infected macrophages were exposed to activating stimuli, the parasites were rapidly killed and digested. Activation of macrophages was obtained by incubation of syngeneic lymphocytes stimulated in mixed cultures containing concanavalin A and endotoxin.

Another NIAID grantee has isolated RNA from highly purified kinetoplast mitochondrial fractions of *Leishmania tarentolae* and has demonstrated that in vivo transcription of 9 and 12S RNA is inhibited by rifampin, but is insensitive to actinomycin D and camptothecin. The kinetoplast seems to be a target organelle of several drugs, and it seems likely that a basic understanding of the molecular biology of the kinetoplast genetic system will aid in the development of a rational chemotherapy.

Leprosy

Leprosy, a major health problem of the developing countries, occurs with a very low incidence in the United States. Because of its worldwide importance and its usefulness as a model of an immunological disease, however, leprosy research continues to be supported by NIAID under the auspices of the U.S.-Japan Cooperative Medical Science Program. There are a total of six grants and three contracts. Research being supported includes in vivo and in vitro cultivation of *M. Leprae*, pharmacology of antileprosy drugs, chemotherapy trials and studies of the basic immunology of leprosy.

Inability to grow *Mycobacterium leprae* and *M. lepraemurium* in cell-free artificial medium (in vitro) has always been a major obstacle to leprosy researchers. The lessons learned from a new culture system for *M. lepraemurim* will be applied to the problem of attaining in vitro cultivation of *M. leprae*.

An NIAID contract with the USPHS Hospital, Carville, has been in effect since July 1975, to supply *M. leprae*-infected armadillo tissues to leprosy researchers (worldwide). The infection rate after i.v. inoculation is 50 to 80 percent, and some of the animals inoculated intravenously with 10^8 or more *M. leprae* are ready to sacrifice for harvest of large numbers of organisms in 1 or 2 years. However, some animals are apparently resistant to infection. This is analogous to the same phenomenon found in humans; some are resistant and others are susceptible. This supply of *M. leprae* from armadillos in numbers not previously available makes it easier to undertake much needed leprosy research.

A number of new chemical methods have been developed to study tissue and plasma levels of the leprosy treatment drugs, Dapsone (DDS) and Rifampin (RFM). In the studies of armadillos infected with *M. leprae*, it was demonstrated that dose and plasma levels of DDS were linearly related, so these studies provide some information needed for chemotherapeutic trials using DDS in infected armadillos. In addition, an assessment was made of the use of saliva as a noninvasive means of monitoring DDS levels in man; preliminary studies indicated an excellent correlation between plasma and saliva levels of DDS. The pharmacokinetic relationships for DDS and RFM that have been established both in man and in animals should be applicable and useful for monitoring levels in various clinical and experimental situations.

A major international effort to develop a vaccine against leprosy is being carried out in conjunction with the IMMLEP program of the WHO Special Programme for Tropical Disease Research. The basic concept for this vaccine is that while the majority of patients with leprosy develop a tuberculoid form in which cell-mediated immunity develops and self-healing ultimately ensues, a minority, generally on the order of 10 percent, develop the lepromatous form of the disease characterized by a selective anergy to antigens of the lepra bacillus. It is in these patients that organisms grow to very high concentrations and represent a prime source of contagion of this disease. If immunization could prime or

sensitize for the satisfactory development of a cell-mediated immune response to the lepra bacillus upon infection, then possibly a noninfectious tuberculoid form of infection would ensue.

As with other research activities supported by NIAID, the extramural component is by far the largest. Most of the program supports free-ranging research, with much smaller efforts in the form of contracts channeled into designated areas to provide answers to specific questions, develop reagents, or test vaccines, etc. No particular efforts are made to coordinate extramural with intramural research, at least over the short run. Extramural program officers try to keep in touch with their counterparts in other U.S. Government agencies that support research in tropical medicine, such as the Army and Navy, or private foundations.

Several additional components of the extramural program (Development and Applications Branch) deserve special mention because they specifically involve activities on an international scale or studies in a foreign country. These include:

1. A contract with St. Jude Children's Research Hospital in Memphis, Tennessee, for worldwide surveillance of animal influenza viruses. This is accomplished through a worldwide network of collaborating laboratories. The rationale for this program is that major antigenic shifts of new human pandemic strains of influenza viruses may have resulted from recombination of strains in nature, including animal influenza viruses. This project interfaces with the U.S.-U.S.S.R. Cooperative Program on Influenza referred to later in this report.
2. The NIAID has had a contract with the Central Public Health Laboratory in Helsinki, Finland, since 1974 (renewed for 3 years in 1977) for evaluation of efficacy of group A meningococcal and *Hemophilus influenza* polysaccharide vaccines in children.
3. Several viral hepatitis projects in foreign countries are supported by contracts with the New York Blood Center. One of these involves work on an experimental hepatitis B vaccine in chimpanzees in Liberia, Africa, where some of these scarce animals are available. The other is a trial of hepatitis B immune globulin in the Far East for prevention of transmission of hepatitis B from pregnant carrier mothers to the fetus.

Individual members of the extramural program serve as members of ad hoc or expert committees, panels, etc., for the World Health Organization and other agencies with international health activities.

Intramural Research Program

The intramural research program for tropical and parasitic diseases consists mainly of the research conducted by the Laboratory of Parasitic Diseases (LPD), if the subject area is interpreted very strictly. However, since the tropical diseases include rickettsial and other tickborne

diseases under study at Rocky Mountain Laboratory (RML), as well as the virus-caused diarrheal diseases, especially the rotaviruses, which are studied in the Laboratory of Infectious Diseases (LID), these two labs should be included. The Laboratory of Microbial Immunity (LMI) is another intramural unit with a research program that deals with immunology of parasitic infections in experimental models. Viral hepatitis, while not a tropical disease problem in the strict sense, is a very important and substantial portion of the LID research program. Furthermore, the viral hepatitis research of LID has extensive international activity, as is detailed below. However, for purposes of fiscal analysis, hepatitis is not included.

Legislative authority for intramural research, as with the extramural program, comes from the Public Health Service Act of 1955 Public Law 81-692, Title III, Part A, Section 301, and Title IV, Part D, Section 431, which deal with creation of additional Institutes of NIH. Also Public Law 86-610, Section 2, clause 1, contains the statement "to advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research, and research training."

To indicate in somewhat greater detail the nature and extent of intramural research programs, several with international involvement are described below. These include the following:

1. Study of gamete immunity in man in Africa by investigators of LPD and LI.
2. Tropical pulmonary eosinophilia and immunology of filariasis in India — LPD.
3. Immunology of Chagas' disease in Brazil — LPD.
4. International collaboration on hepatitis virus research — LID.
5. International collaboration on viral gastroenteritis — LID.

Gamete Malarial Immunity

In view of the experimental work in LPD on the immunogenic effect of avian and simian malarial gametes, which could be demonstrated by the failure of gamete-immunized animals to be infective for mosquitoes, it seemed important to examine this question in humans in an endemic area. In other words, in areas where malarial transmission is holoendemic, is there evidence of natural gamete immunity? Several investigators of LPD and one from LI studied this question during a stay of several months at the United Kingdom's Medical Research Council Laboratory in Gambia, West Africa. They found that sera from adult immune Gambians did not react with surface antigens on *P. falciparum* gametes using the IFA technique, nor did their sera block cyst formation by gametes of *P. falciparum* in the mosquito. During this same visit it was possible to collect additional strains of *P. falciparum* for future work at NIH.

Tropical Pulmonary Eosinophilia

An investigator from LPD made a second annual trip of several weeks to Madras, India, for work with collaborators at the Tuberculosis Chemotherapy Center and Medical College and General Hospital of Madras on tropical pulmonary eosinophilia (TPE) and on filariasis. This is an area of the world where TPE and filariasis are both relatively common. The former is believed to be a variety of filarial disease in which the human host traps the microfilariae that otherwise would circulate in the blood. There is no definite proof that TPE is really a filarial infection, and if so which species (human or animal) of filarial parasite is involved, nor do we know the immunologic mechanism by which the putative trapping of microfilariae occurs. The condition of TPE is associated with very high levels of circulating eosinophils and IgE antibody.

By using the histamine release reaction prompted by the exposure of circulating basophils from peripheral leukocytes of the blood to a specific antigen that reacts with IgE coating the surface of the basophils, it is possible to test for specificity of the IgE response in these patients. The histamine released is measured with an exquisitely sensitive and specific radioimmunoassay. These studies have shown that the white cells (basophils) of patients with TPE release maximum histamine to microfilarial antigens of human filarial parasites when exposed to various filarial antigens. Thus, it appears that the symptoms and signs of TPE can be explained as an allergic (immediate) hypersensitivity reaction to human microfilarial antigens. A number of other important questions involving the host immunologic response in filarial infections have been raised by this investigation, as well as questions concerning the importance of the chronic lung disease which TPE constitutes. This collaborative project, it should be noted, was initiated as an exploratory P.L.-480 project and with considerable help from the Fogarty International Center.

Immunology of Chagas' Disease

The principal manifestation of Chagas' disease is a cardiomyopathy that occurs some years after initial infection with the parasite *Trypanosoma cruzi*. Another chronic sequel to infection with *T. cruzi* is involvement of the esophagus with dilatation and malfunction that is seen in some areas of Latin America and not in others. Both of these features of Chagas' disease are important health problems in many regions of Latin America, but the prevalence of the disease, as well as presence or absence of the megaesophagus, has a spotty distribution that cannot easily be explained by different strains of the parasite or degree of exposure to vector bugs, or by frequency of infection with the parasite, as measured by antibody tests. Thus, there are many reasons to question whether differences in host response might account for presence or absence of chronic disease. With these issues in mind, and because of

previous laboratory work relating to these problems, several investigators of LPD initiated a collaborative project with physicians at the Faculty of Medicine of Federal University of Goiás in Goiania, Brazil. This is a region of Brazil where the megaesophagus and cardiomyopathy of chronic Chagas' disease are common.

Two questions were investigated: one, cell-mediated immune response to several different antigens prepared from *T. cruzi* in patients with chronic disease and in appropriate control groups, and second, evidence of genetic influence over development of chronic Chagas' disease by HLA-tissue typing. To carry out the HLA-typing, it was necessary to have the assistance of a former research fellow now in Brazil who had trained with the tissue typing group at Duke University, as well as support from the NIAID extramural program to supply typing trays and many of the typing antisera. A final crucial element to this collaborative research project was the logistical and financial support of the Pan American Health Organization (PAHO).

Results of the study showed that patients with chronic Chagas disease exhibited no unusual cell-mediated immune response to *T. cruzi* antigens. They reacted to the same degree as individuals infected with the parasite (positive blood test) but with no evidence of disease. Specificity of the parasite antigens for blastogenic response was established and the most reactive antigen was identified. The HLA-typing showed an interesting concentration of one A-locus type among patients with chronic disease, as compared to controls, and a relative infrequency of another A-locus type. However, this association of HLA-type with Chagas' disease was not sufficiently strong for critical statistical evaluation. It will be necessary to increase the numbers of patients studied and this project will be expanded to see if the HLA relationship holds.

Hepatitis Virus Research

The hepatitis viruses are ubiquitous agents that are highly endemic in the developing parts of the world. They are equally prevalent in developing countries situated in tropical and subarctic climates.

The Hepatitis Viruses Section of the Laboratory of Infectious Diseases has carried out an active program of collaborative research on viral hepatitis with many groups throughout the world. Among these have been studies of the immunopathology of hepatitis B virus infection, with a laboratory in Germany, and with investigators in Poland and Greece on epidemiology of viral hepatitis. There are collaborative studies of new and unique antigens associated with hepatitis B virus infection with a worker from Italy and surveys of prevalence of antibody to hepatitis virus being done in collaboration with workers in Russia, Denmark, and Sweden.

Other collaborative studies include an examination of epidemics of viral hepatitis in India, studies of hepatic cell carcinoma in Taiwan, characterization of the hepatitis A virion with an investigator in Japan,

and the seroepidemiology of type A hepatitis in Kenya. Collaborative studies of viral hepatitis are in progress or in the planning stage in Argentina, Brazil, Venezuela, and Costa Rica.

Other areas of the world where collaborative work on virus hepatitis is being carried out include Australia and islands of the South Pacific. Further knowledge on the seroepidemiology of types A and B hepatitis in the South Pacific is of particular interest because it might be possible to test hepatitis B vaccines in certain islands in the South Pacific where their isolated nature offers unique opportunities to test the possibility of eradication of hepatitis B viruses from the isolated populations.

Viral Gastroenteritis

Enteric diseases continue to be a major cause of morbidity throughout the world and a major cause of morbidity and mortality in the developing countries. The NIAID Laboratory of Infectious Diseases is engaged in many collaborative studies with investigators in various parts of the world; these studies are aimed at elucidating the etiology of gastroenteritis with special emphasis on the role of viral pathogens.

The LID continues its studies with the World Health Organization on the etiology of diarrhea. Thus far, stool specimens from infants and young children have been tested from the following countries for the presence of rotaviruses and the Norwalk agent: Tunisia, Senegal, Korea, Hong Kong, Uganda, Zaire, Malaysia, Singapore, Central African Republic, French Guiana, and Sri Lanka. Rotaviruses have been found to be an important agent of diarrhea in this age group, whereas the Norwalk agent has not. In addition, certain specimens have also been examined for the presence of adenoviruses. Only a limited number of paired sera are available from this study.

The LID continues its collaboration with investigators in the Cholera Research Laboratory in Bangladesh on the etiology of gastroenteritis. These studies, which are many-faceted, include family studies on the etiology of diarrheal illnesses in villages in Bangladesh as well as studies of the etiology of diarrheal illnesses in malnourished groups.

The LID also has collaborated with investigators from Guatemala in studying stool specimens from infants and young children from the Guatemalan highland village of Santa Maria Cauque. A population of 24 infants and young children who had been studied previously during the first 3 years of life was studied employing newly available methods for the occurrence of rotavirus and Norwalk infection. Infection with rotavirus was associated with 26 (14.2 percent) of 183 selected diarrheal episodes. However, rotavirus infection was documented in over 50 percent of the dehydrating episodes studied, thus further indicating the importance of rotavirus infection in this population. In addition, this study indicated that sequential episodes of diarrhea were associated with two different rotavirus serotypes. The Norwalk agent was not detected.

In additional collaborative studies of the LID, the Norwalk agent was shown to be associated with a gastroenteritis outbreak in Japan. Also, collaborative studies with Australian investigators have confirmed the association of Norwalk infection with a large outbreak of gastroenteritis associated with the ingestion of oysters.

The worldwide prevalence of antibody to the Norwalk agent has been investigated collaboratively in a preliminary fashion by studying sera from Belgium, Yugoslavia, Switzerland, Ecuador, and Nepal. In addition, the role of the Norwalk agent in travelers' diarrhea has been investigated by studying specimens from Peace Corps workers in Kenya, Morocco, and Honduras. Finally, the LID is engaged in studies of antibody to *E. coli* LT using an RIA-BL test with serum specimens from Peace Corps workers in Kenya, and in inhabitants of Bangladesh.

In addition to the specific research projects, such as those outlined above, which are conducted abroad by NIAID investigators or by their direct collaborators, many Institute scientists are involved indirectly in international activities. A number of investigators serve on expert committees or panels of agencies (WHO, PAHO, Rockefeller Foundation, etc.), or are asked to attend scientific meetings that deal with health problems of foreign countries. Virtually all of the intramural laboratories have Fogarty visiting fellows from foreign countries working in the labs who receive research training for a period of 1 to 3 years and then return to their country. For example, during FY 1978, there were 39 such visiting fellows from 15 countries working in the intramural laboratories. Finally, some intramural scientists collaborate with colleagues abroad on specific research problems by exchange of information, use of special techniques, etc., such as one who collaborates with scientists in France on regulation of transcription of SV-40 virus.

Several of the intramural laboratories serve as reference centers for WHO in specific subjects, such as the RML for rickettsial diseases and LID for respiratory viruses other than influenza, and for mycoplasmas.

Scientists from foreign countries frequently work in intramural laboratories under other auspices than the Visiting Fellow Program. Their appointments may be on a more senior level, such as visiting associates or visiting scientists, or they may come for short periods as guest workers supported by funds from their own country. There were 18 visiting associates and/or scientists in the Institute during FY 1978 from 10 different countries.

Finally, some of the intramural scientists are involved in research projects supported by P.L.-480 funds, or funds from bilateral programs.

The U.S.-Japan Cooperative Medical Science Program

The U.S.-Japan Cooperative Medical Science Program was initiated in January, 1965, as the result of a meeting between the Prime Minister of Japan and the President of the United States. It was agreed that the two countries would undertake a joint cooperative research

effort in biomedical sciences to improve the health of the people of Asia. The disease categories considered to be of particular importance included cholera, leprosy, malnutrition, parasitic diseases (schistosomiasis and filariasis), tuberculosis, and viral diseases (rabies, dengue hemorrhagic fever, and other selected arbovirus diseases). In 1972, environmental mutagenesis and carcinogenesis was added as a seventh category.

Under Public Law 86-610, the International Health Research Act of 1960, the President delegated the responsibility for foreign policy and foreign relations of the program to the State Department and for its scientific conduct to the Department of Health, Education, and Welfare; the latter delegated this responsibility to the National Institutes of Health. In 1968, the conduct of the program was transferred from the Office of International Research to the National Institute of Allergy and Infectious Diseases, where it remains today.

The U.S.-Japan Cooperative Medical Science Program operates within a bilateral governmental framework. Nevertheless, it may involve scientists and facilities in third countries and/or collaboration with international or other organizations. The relevant regions in Asia, although not specifically defined, are generally understood to include the Republic of Korea on the north, India and Pakistan to the west, and other adjacent nations in the broad Pacific basin.

Each country supports the cost of its own research. At the National Institutes of Health, grants submitted for doing research on the disease categories of the U.S.-Japan Cooperative Medical Science Program compete with all other grants based on scientific merit, and if funded are appropriately assigned. However, there is no special fund allocation for this program. Contracts are awarded by each Institute based upon need and availability of funds. Support for the program is provided by four Institutes. Research on cholera, leprosy, parasitic diseases, tuberculosis, and viral diseases is supported by the National Institute of Allergy and Infectious Diseases. Malnutrition research receives support from the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Child Health and Human Development. Research on environmental mutagenesis and carcinogenesis is funded by the National Institute of Environmental Health Sciences. Total funding for grants and contracts during FY 1978 was \$11,460,910. A summary of these expenditures is found in table 3.

The notable success of the program, involving close research planning and scientific collaboration with many different investigators in Japan, may be attributed to careful selection and continuing review of research objectives within each of the stated disease categories. During calendar year 1978, the joint committee, comprising the United States and Japanese delegations, approved the review and evaluation reports for the Parasitic and Viral Diseases Panels, and initiated the review process for the Environmental Mutagenesis and Carcinogenesis Panels, which will be completed in 1979. A very successful symposium on hepatitis was held in Tokyo. The joint committee approved in principle the formation of a new program on hepatitis pending development of acceptable

**Table 3. U.S.-Japan Cooperative Medical Science Program
Grants and Contracts FY 1978**

Disease Category	Number Grants	Dollar Amount	Number Contracts	Dollar Amount
Cholera	16	\$ 834,000	4	\$ 309,000
Environmental mutagenesis and carcinogenesis (a)	48	3,850,000	8	1,500,000
Leprosy	6	577,000	3	230,000
Malnutrition (b)	12	1,072,000	1	19,000
Parasitic diseases	26	1,676,000	4	254,000
Tuberculosis	4	261,000	2	134,000
Viral diseases	6	744,910	0	--
Totals	118	\$9,014,910	22	\$2,446,000
Total Grants and Contracts				\$11,460,910

(a) Supported by NIEHS (\$5,350,000)

(b) Supported by NIAMDD and NICHD (\$1,091,000)

All others supported by NIAID (\$5,019,910)

guidelines. The Malnutrition Panel's guidelines were revised to include the health consequences of differing dietary patterns and food habits. This area has application not only to Asia but to all parts of the world.

Cooperation with the World Health Organization in research on schistosomiasis, filariasis, and leprosy has been initiated and efforts to strengthen this association continue. The program continues to explore ways for developing additional linkages with domestic and foreign organizations interested in international biomedical research.

International Centers for Medical Research Program

The International Centers for Medical Research Program was established at the National Institutes of Health under the authority of Public Law 86-610, the International Health Research Act of 1960. The program operates within this law under Section 2, subsection (1) "to advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research, and research training." The scientific supervision of the ICMR program was under the Office of International Health from 1960 until 1968, when this responsibility was transferred to NIAID.

The ICMR grants are funded for 5 years, with the last award being made in May 1975. However, continuation is based upon a satisfactory

annual review of each unit's scientific progress. This program, which has been operative since 1960, will be supplanted by a new international initiative in 1980. Unlike the present ICMR program, which has included areas of research other than infectious diseases and immunology, the new program, International Collaboration in Infectious Diseases Research, will be tightly focused on infectious diseases and the immunology of these diseases. In addition, infectious diseases research will be limited to diseases of health importance in developing countries. However, in the past 2 years, the ICMR units have made a concerted effort to emphasize infectious diseases research.

The ICMR program has as its principal objective the provision of high quality research and scientific opportunities for Americans in the broad fields of tropical medicine and in response to the special opportunities existing within each ICMR framework. The length of the research period overseas is a discretionary concern of the ICMR program director and is obviously determined by both the interests of the prospective investigator and the specific opportunities available within the given ICMR unit. Consistently, the emphasis is upon the quality rather than the quantity or duration of the research programs.

The aggregate ICMR units serve as a national resource for utilization by senior, as well as less experienced, scientists to create a comparatively modest pool of investigators with a sustained career interest in international or geographic biomedical research. In this regard, the ICMR program directors are encouraged to establish a selective, interdisciplinary scientific program. Their activities encourage and accommodate a number of parent university departments other than the one that primarily sponsors the ICMR operation. Also, interested and qualified investigators from other universities may be invited to spend all or part of a sabbatical leave performing pertinent research at one of these units. As far as is possible, the ICMR core grant is used for research support at the offshore ICMR site, rather than at the parent domestic university. In FY 1978, the total expenditures of the four ICMR grants was about \$2,117,000.

Discussion of the four institutions participating in the ICMR program at present and their respective areas of research interests follows:

1. *The University of California* ICMR in San Francisco with its overseas site in Kuala Lumpur, Malaysia, is under the direction of Dr. Albert Rudnick. Current research interests include continuation of the studies of the jungle cycle of dengue and the importance of this jungle reservoir as a source of infection in man. Studies in the community health section include population dynamics, fetal wastage and infant mortality, the behavioral aspects of communicable diseases hazards, medical anthropology, and traditional Chinese medical practice. The human genetics and hematology section is concerned particularly with abnormal hemoglobins. The parasitology section is studying the host-parasite interactions in relation to biocontrol of trematode infections in snails.

2. *The Johns Hopkins University* ICMR in Baltimore has an overseas site in Dacca, Bangladesh, and more recently, one in the Panama Canal Zone at the Gorgas Memorial Laboratories. With the proposed internationalization of the Cholera Research Laboratory, ICMR research has been reduced. Only one investigator remains to complete his research. The major portion of the effect has been transferred to Gorgas. The emphasis continues on various aspects of diarrheal research. The program director is Dr. Bradley Sack.

3. *The University of Maryland* ICMR in Baltimore and Lahore, Pakistan, is under the direction of Dr. Richard Baker. Research in Lahore is centered around an integrated program on the genetics and field ecology of mosquito vectors. Efforts are directed toward biological control of the vectors of malaria and selected arbovirus infections.

4. *Tulane University* in New Orleans has an overseas ICMR unit in Cali, Colombia, which is concentrating its efforts in infectious diseases and immunology. The nutritional, behavioral science, and social epidemiology projects have been or are in the process of being phased out. Investigators are pursuing projects in parasitology, bacteriology, and virology. This unit is host to Peace Corps volunteers who receive training in field work activities. Investigators from other institutions in Colombia and the United States are collaborating on a number of research projects. Dr. Thomas Orihel is the program director.

Special Foreign Currency (P.L.-480) Programs

The P.L.-480 research projects are arrangements by which an individual or research group in designated countries is granted the use of U.S.-owned local currency from funds generated by purchase of commodities, such as wheat, supplied by the United States. The project is linked to an individual or group in the United States, with a designated project officer who is expected to supply scientific collaboration, assistance, or advice for the project. Legislative authority for P.L.-480 projects is derived from Section 104 (b) (3) of Public Law 480, 83rd Congress and Section 37 P.L. 86-610.

Intramural or extramural scientists serve as project officers for P.L.-480 projects. The following projects were in effect during FY 1978:

1. In Egypt – Tick, vertebrate, and infectious agent interrelationships
project officers – Drs. Clifford and Kierans of RML
2. In Egypt – Tick-borne viruses in vector and host cells
project officer – Dr. Yunker of RML
3. In Egypt – Epidemiology of meningitis due to *H. influenzae*
project officer – Dr. Hill of Extramural

4. In Poland — Cytophilic antibody and transfer of skin reactions
project officer — Dr. Munoz of RML

Other NIAID Programs Involving International Activities

The U.S.-U.S.S.R. Cooperative Program on Influenza

This program is in its fourth year and is essentially a framework for scientific communication between the two countries in the subject area. It provides for exchange of information, scientific meetings and visits by scientists, exchange of virus strains and reagents. Personnel from the Extramural Program of NIAID (MIDP) serve as coordinators for several of the problem areas of the program.

Support for the Cholera Research Laboratory or U.S.-Bangladesh Agreement

This program supports research on cholera and related diarrheal diseases initiated in 1960 with quite heavy NIAID support and involvement initially, but with subsequent modifications in the extent and nature of the support in recent years. The facility supported is in Dacca, Bangladesh (formerly East Pakistan). It is staffed by scientists from the host as well as foreign countries, and receives support from the governments of the United Kingdom and Australia as well as the local government.

Funding is provided by a Participating Agency Service Agreement (PASA) with the U.S. Agency for International Development (AID). Scientific management, administrative support, and supplies are provided by NIAID.

Scientific aspects of the work at the Cholera Research Lab are coordinated with other research on cholera and diarrheal diseases supported by the extramural program of NIAID.

Reagents Program for Human Tissue Typing

The Immunology, Allergy, and Immune Diseases Program (IAIDP) of NIAID initiated a program of HLA tissue typing as a central supplier of antisera some years ago. This program serves a practical need for organ transplantation and does basic immunological research. For example, in FY 1978 the NIAID supplied more than 3,000 vials of HLA-typing sera to about 150 non-U.S. laboratories.

The IAIDP supports periodic international workshops to review and disseminate most recent knowledge of the HLA system in man. At these workshops new reagents are tested. A serum bank for mouse histocompatibility antigens is also maintained by the program for basic

research in experimental work on genetics of the immune response and transplantation. These reagents are also supplied to qualified investigators outside the United States (59 in FY 1978).

HLA-typing reagents were made available by the reagents program to an intramural research project of the Lab of Parasitic Diseases in Brazil investigating the possible association of HLA types with chronic Chagas' disease.

The National Institute of Arthritis, Metabolism, and Digestive Diseases

The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) is responsible for the conduct and support of biomedical research relevant to a wide range of chronic, disabling disorders. A number of Institute-funded research activities draw upon the talents and investigative expertise of the international scientific community. This report highlights the nature and scope of collaborative and individual research efforts carried out with NIAMDD support as integral parts of the Institute's overall mission.

Malnutrition Program of U.S.-Japan Cooperative Medical Science Program

Program Background

The U.S.-Japan Cooperative Medical Science Program was established in 1965 under Public Law 86-610. Medical advisers from both countries met in Tokyo in April 1965 and selected cholera, leprosy, parasitic diseases, tuberculosis, and viral diseases as initial health problems for joint research. Malnutrition was added to the program in 1966. Malnutrition was recognized as contributing to increased mortality, morbidity, and infections—particularly in infants and children. The imbalance of food production and population growth was viewed as contributing to malnutrition and as one of the serious health problems of people in Asian countries.

Since its inception, the Malnutrition Panel has concentrated on research dealing with problems of protein-calorie undernutrition; anemia; vitamin A deficiency; improving low-cost protein foods; toxic substances in plant food (mycotoxins); and the effects of malnutrition on physical growth, mental development, and performance. The panel has held symposia almost every year on special priority topics as stated in joint scientific guidelines. These meetings have been attended by many scientists from other countries in addition to the United States and Japan.

The priority areas have been revised and modified from time to time, depending on advances in research and need for change of direction and emphasis. Cooperation with other agencies having similar interest in malnutrition research has also been actively pursued. Liaison members of the U.S. Malnutrition Panel include representatives from the United States Agency for International Development, Pan American Health Organization, and other NIH Institutes. In addition, staff from other agencies (United States Department of Agriculture, Health and Nutrition Examination Survey, and Center for Disease Control of the U.S. Public Health Service) have been invited to some panel meetings.

The Institute is endeavoring to strengthen its international nutrition research activities that are involved in the U.S.-Japan Cooperative Medical Science Program. Support given to the Malnutrition and Anemia Center at Chiang Mai, Thailand, for 10 years has produced a facility through which many aspects of malnutrition can be studied much more effectively than in the United States.

Since 1965, the Malnutrition Program of the U.S.-Japan Cooperative Medical Science Program has been the primary avenue through which international research activities in nutrition are supported. Accomplishments of the U.S. Malnutrition Program in FY 1978 included the support of research projects in previously identified priority areas, individual and joint panel meetings, symposia, and publications.

Specific research projects, carried out abroad among populations with severe nutritional deficiency diseases, are designed to find solutions to complex malnutrition problems. Since only half of the earth's population is able to maintain an adequate diet, there is a critical need for research to find economically feasible ways and means to transform marginal nutrition and overt nutritional deficiency to adequacy.

Traditionally, the Institute has conducted such nutrition research in developing countries because of the availability of large population groups afflicted with specific nutritional deficiencies that can be readily studied. The results are twofold: the research may stimulate emergence to nutritional self-sufficiency from mere subsistence in developing countries and may also add knowledge of normal nutrition and nutritional deficiencies that will benefit the U.S. population.

The startling realization that malnutrition also exists within our own population lends an element of expediency to nutrition research. By providing scientific know-how for effective use of economical native protein sources, these programs also discourage dependency of developing countries on more progressive countries for expensive protein-rich foods while enabling them to make inroads against protein malnutrition.

Based on the availability of funds, the U.S. Malnutrition Panel fulfills the following objectives: (1) supports scientific projects; (2) organizes, funds, and conducts scientific meetings in the United States; (3) provides financial support to the U.S. Panel members and consultants attending meetings related to the program; and (4) provides staff and operating costs to the U.S. Secretariat. The Japanese ministries of

Health and Welfare and Education assume a similar responsibility for their counterpart activities, i.e., research projects, meetings held in Japan, panel members and consultants, and the Japanese Secretariat.

The total NIH support for nutrition research under the U.S.-Japan Program in FY 1978 was \$1.07 million. NIAMDD provided \$381,779, while the remainder was awarded from the National Institute of Child Health and Human Development. In addition, the NIAMDD supported the Joint U.S.-Japan Panel Meeting and International Conference on Behavioral Effects of Energy and Protein Deficits held in Washington, D.C., in late 1977 by an estimated amount of \$44,024. The International Rice Research Institute was awarded a contract of \$18,834 to complete the nutritional evaluation of improved high-protein rice recently developed in the Philippines under a long-term contract from NIAMDD.

The activities of the panel, administered by the NIAMDD, are a part of the overall U.S.-Japan Cooperative Medical Science Program administered by the National Institute of Allergy and Infectious Diseases, NIH. The Department of State provides formal channels to the Japanese. The overall USJCMSP has both U.S.- and Japanese-appointed delegations, which are jointly responsible for the programs.

Research and Related Activities

Principal aspects of international health cooperation are:

1. Support of research projects that fulfill the current and updated research objectives of the U.S. Malnutrition Panel:
 - (a) influence of environmental and host factors on nutritional requirements;
 - (b) health significance and methods of preventing iron deficiency;
 - (c) interaction of nutrition, immune competence, and infection;
 - (d) health consequences of different dietary patterns and food habits.
2. Support of workshops and conferences to further research important to solving the malnutrition problems of Asian countries.
3. The Joint U.S.-Japan Malnutrition Panels meet annually, alternating between the United States and Japan. The meeting for FY 1978 was held in Washington, D.C., on November 29, the day preceeding the 3-day conference. Simultaneous translation into English and Japanese was provided for the 4 days.

Research on bladder stone disease in children in Thailand involves the daily supplementation of 60 mg of inorganic phosphorus per kilogram body weight. Although it is too early to draw conclusions, no significant difference has been observed in the number of subjects who developed bladder stone disease symptoms between the treated and the placebo groups. However, the percentage of subjects who developed severe symptoms associated with this condition was significantly higher in the untreated group.

Evaluation studies compared the nutritional value of a high-protein vs. conventional low-protein milled rice at levels supplying the same protein intake. Nitrogen balance studies were performed in four Filipino children, eight convalescing Peruvian children, and five Taiwanese men. The genetically improved rice containing more total protein was found to be comparable or only slightly inferior in apparent digestibility and apparent nitrogen retention to low-protein conventional rice. This work shows that the improved high-protein variety has a net protein utilization comparable to that of conventional rice, per unit of protein. Thus, growing children, who require more protein than can be provided with native diets based on conventional rice, fed the rice containing the higher protein level would receive considerably *more* utilizable protein.

Recently, the Malnutrition Panel has redefined its established objectives in accordance with its research progress in these areas. In addition, the panel has begun serious examination of the potential scope of its new objective, "health consequences of different and changing dietary patterns and food habits." This topic was the basis for planning a joint U.S.-Japan Malnutrition Workshop in December 1978 (FY 1979).

U.S.-U.S.S.R. Cooperative Program in Arthritis

A cooperative study of arthritis organized under this program is a fourth major collaborative project in the health sciences between the United States and the U.S.S.R. Through a series of bilateral exchanges of scientific personnel, the program emphasizes clinical studies of the treatment of systemic lupus erythematosus (SLE) and rheumatoid arthritis. Since 1974, ten major meetings have been held, including the most recent meeting in Moscow, October 16-18, 1978. These meetings are supplemented by the exchange of reprints and lecture materials, as well as by discussions of preliminary results and future projects.

The cooperative program in arthritis has its origin in the U.S.-U.S.S.R. Health Exchange Program of 1972, a joint agreement designed to improve collaboration between the two countries in the field of public health and medical science. On September 7, 1973, arthritis became the fourth area of concentration in the program through a joint announcement of then-Secretary of HEW Caspar W. Weinberger and Soviet

Minister of Health Boris V. Petrovsky. In FY 1978, NIAMDD funding in support of the program totaled \$234,809.

In December 1976, the United States and the U.S.S.R. began their first cooperative clinical trials in the field of arthritis. Physicians in both countries are now conducting identical studies on the use of D-penicillamine in rheumatoid arthritis. Clinical trials in Great Britain have supported its efficacy in treating serious forms of the disorder. On November 8, 1978, D-penicillamine was approved by the U.S. Food and Drug Administration for the treatment of severe, active rheumatoid arthritis that has failed to respond to more conservative treatment. In the present U.S.-U.S.S.R. cooperative study, lower doses of the drug are being compared for effectiveness with the generally prescribed higher doses in an effort to reduce the incidence of adverse side effects.

Dr. Israeli Jaffe of the New York Medical College and Drs. John Decker and Paul Plotz of the Arthritis and Rheumatism Branch of the NIAMDD are coordinating the U.S. cooperative trial in four New York medical schools. In the Soviet Union, studies are under way at the Institute for Rheumatism of the Academy of Medical Science in Moscow under the direction of Professors M.G. Astapenko and E. Agababova. The effectiveness of treatment over a 1-year period will be evaluated, and analysis of the data will begin in January 1980.

Research Emphasis

The Fifth Working Meeting of the U.S.-U.S.S.R. Cooperative Program was held in October 1978 in Moscow. At this session, the program participants discussed progress in clinical studies of SLE, rheumatoid arthritis and juvenile rheumatoid arthritis, progressive systemic sclerosis (scleroderma), and hand function in rheumatoid arthritis. In addition, virological and immunological studies will continue to explore the mechanisms at work in SLE, rheumatoid arthritis, and progressive systemic sclerosis.

Future work plans for these areas emphasized exchange of scientists, data collection and pertinent technical information, and the continuation of clinical studies of patients with these disorders. The U.S.-U.S.S.R. program collaborators will meet in the United States in the spring of 1980 to assess results of ongoing studies and to discuss future plans for expansion of research in certain problem areas.

Bone Diseases Program

The Bone Diseases Program of NIAMDD currently supports a long-term research effort headed by investigators at the Hadassah University Hospital in Jerusalem, Israel. These scientists are studying the effect of prolonged administration of a combination of calcium, phosphate, and fluoride salts on bone structure and density in middle-aged

patients with osteoporosis. Another aspect of this effort is an investigation into the relationship between long-term levels of intake of various dietary components and the prevalence and severity of osteoporosis among patients with different ethnic backgrounds, geographic origins, and dietary customs. The unique population makeup of this country provides an optimal opportunity for this type of study.

Also included in this project is development of new techniques of early diagnosis of osteoporosis through bone densitometry sophisticated enough to discern minimal changes in bone density particularly in the spinal vertebrae. A study of the possible prophylactic and therapeutic roles of the recently defined biologically active metabolites of vitamin D rounds off this comprehensive project in osteoporosis.

Kidney, Urologic, and Blood Diseases Program

The Kidney, Urologic, and Blood Diseases Program of the NIAMDD currently supports in foreign countries three research grants totaling \$132,855, and ten research and service contracts in the amount of \$572,964.

Among the grantees, investigators at the Mahidol University in Bangkok, Thailand, are analyzing genetic defects in the thalassemias and related hemoglobinopathies, and studying interactions between the various genes and between genes and environmental factors.

Another grantee investigator, Dr. Robert Williamson, of St. Mary's Hospital Medical School at the University of London, is a leading international expert in the control of hemoglobin biosynthesis and genetics. He is studying the composition of genes determining the structure of hemoglobin, and the interaction of those genes with neighboring genetic material.

Research carried out by NIAMDD contractors abroad extends from basic chemical studies to an unusual group of investigations conducted by three different research teams in Germany to compare the efficacy of postdilution hemofiltration with conventional hemodialysis. The former method of treating patients with chronic renal insufficiency was developed by Dr. Eduard A. Quellhorst of the Nephrological Center Niedersachsen in West Germany. It is being studied there, in conjunction with studies in the United States, because of the existence in Germany of a base of research (patients regularly treated with hemofiltration and hemofiltration machines) in this field available nowhere else in the world.

Another example of research supported abroad under contract is the screening program on populations of uremic patients and subsequent analysis of "middle molecule" (a suspected group of toxins in anemia) data that are being studied in relation to diagnosis, protein intake, incidence of various uremic and nonuremic complications, different biochemical variables in plasma, residual renal function, and dialysis index. The Institute has funded this work by Dr. Jonas Bergstrom, who is known worldwide for these important investigations.

The work of Dr. Dimitrios G. Oreopoulos of Toronto Western Hospital in Canada is another contract-supported investigation abroad. Dr. Oreopoulos treats the largest patient population maintained by peritoneal dialysis in the world. NIAMDD-sponsored investigations of the novel technique known as continuous ambulatory peritoneal dialysis (CAPD) were contracted with him because of his great experience, remarkable and original innovations, and access to such a large population of suitable patients. CAPD appears to be on the brink of becoming a significant mode of maintenance treatment in chronic renal failure, and the studies of Dr. Oreopoulos' team are now directed toward lowering the incidence of peritonitis, defining the ideal composition of the dialysate for this therapy, and improving the connection through which solution is introduced into the abdominal cavity.

Diabetes, Endocrine and Metabolic Diseases Program (DEMD)

Since the passage of the National Diabetes Mellitus Research Education Act in 1974, emphasis on this segment of the Institute's overall research effort has increased significantly. While not in the context of one specific program, 18 international research projects were supported in FY 1978 by the Institute's Diabetes, Endocrine, and Metabolic Diseases Program in the amount of \$752,685.

In addition, the DEMD program supported a workshop on diabetes at the international level. A major problem in the assessment of its impact is the lack of a satisfactory diagnostic and classification scheme for the various forms of diabetes. To address this issue, the Institute's National Diabetes Data Group sponsored, in FY 1978, an international work group that formulated a consensus on a functional classification of diabetes, and on appropriate uniform criteria and nomenclature to be used as a guide for clinical and epidemiological research information. This classification has been widely circulated among the international diabetes community for comment.

FY 1978 Foreign Awards in the Diabetes, Endocrine, and Metabolic Diseases Program

Visiting Scientists Program

A description of the international activities of NIAMDD would be incomplete without reference to the very important impact exerted by the appointment of qualified scientists from abroad to work in the Institute's laboratories and clinics in Bethesda for various periods of time, and reciprocal arrangements for NIAMDD scientists to visit and work in collaborating laboratories and clinics abroad.

Some of these arrangements fall into the framework of formal bilateral scientific collaboration agreements between the United States

and other countries, primarily in Europe; others represent longstanding informal arrangements between a number of laboratories throughout the world and the intramural program of NIAMDD. This exchange of high-caliber scientists across national boundaries with constant opportunities for cross-fertilization of new ideas and biomedical techniques has been mutually beneficial for many years and is expected to continue providing significant scientific dividends in the future.

Outlook

The NIAMDD plans to continue its international involvement in research in order to capitalize on the scientific expertise, as well as the unique research settings, available throughout the world. Only through open communication and pooling of research knowledge can we hope to control, prevent, and ultimately eliminate the many diverse disorders that fall within the Institute's investigative responsibilities.

National Institute of Child Health and Human Development

Introduction

The NICHD views the development of international relationships in the biomedical and behavioral sciences as crucial to the pursuit of new knowledge in the field of maternal-fetal-child-family development. The Director of the Institute serves as the focal point for all international activities, which range from cooperative bilateral health agreements (to facilitate scientific exchange) to support of and participation in international meetings, conferences, and seminars. During the reporting period, the Institute supported 31 international research projects totaling \$2,039,060; 12 program projects totaling \$601,725; 6 research contracts totaling \$486,175; and 2 intramural projects totaling \$49,000. A grand total of 51 projects were supported at a total of \$3,175,960. These programs were funded through the Institute's Center for Research for Mothers and Children (CRMC), Center for Population Research (CPR), Epidemiology and Biometry Research Program (EBRP), and Intramural Research Program (IRP), and are discussed in detail in the section that follows.

Major Programs and Activities

Epidemiology and Biometry Research Program (EBRP)

The Biometry Branch of the EBRP currently oversees two bilateral health projects.

The first is a contract and collaborative research project under P.L.-480 funding with the Mother and Child Institute of Warsaw, Poland. The project, initiated in April 1976 and completed in December 1978, involves a study of the effects of induced abortion on subsequent pregnancy outcome. Thus far, analyses have focused on modes of termination of pregnancy, birthweight of live borns, age of mother, education, smoking, height, types of medication taken during pregnancy, number of previous pregnancies, abortions, and interruptions. Since therapeutic abortion is the predominant method of birth control in many countries and is increasing in frequency in the United States, the effect of abortion procedures on subsequent pregnancy outcome is a question of utmost importance that deserves to be answered.

The second is a contract and collaborative research project with the University of Trondheim, Norway. The project, "Outcome of Successive Pregnancies for Norwegian Women, 1967-1976," was initiated in August 1978 and is still in progress. The contract relies upon a unique data base to study some statistical aspects of repeating premature or mature births in a well-defined national cohort of mothers. This study will contribute to research aimed at elucidating factors that predispose to preterm or low birth weight delivery. Infant mortality will be studied as it relates to prematurity and the tendency to repeat similar gestational age and birthweight in subsequent deliveries to the same mother. This tendency to repeat premature delivery is one of the strongest predictive associations known from previous studies of the epidemiology of prematurity.

Center for Population Research (CPR)

The CPR is participating in numerous important contracts and grants involving international research activities. During FY 1978, the center's international projects totaled 34. Examples of the major international research projects supported by CPR in FY 1978 are summarized below.

Investigators at Johns Hopkins University are conducting a study in Taiwan to determine whether any association exists between oral contraceptive usage and increased risks of stroke among married women of childbearing age in a developing country.

A grant to the University of Southern California is supporting a study to determine the effect of family size and child spacing upon the health and social development of children and their mothers, involving a Danish population of 9,000 children born in Copenhagen between 1959 and 1961.

Using data from Canada, the Dominican Republic, Colombia, and Chile, investigators at Northwestern University conducted a study to develop and test econometric models relating to fertility and female labor force participation over the life cycle. The aim of the study was to provide an econometric framework for the analysis of population problems. The final report is being completed.

A grant to the Transnational Family Research Institute is supporting a 1-year study to ascertain sociodemographic characteristics and frequency distributions associated with specific patterns of pregnancy resolution for all women in Denmark ages 13-18 and, where possible, their male partners. Nationally representative data on the determinants of patterns of adolescent pregnancy resolution are difficult to obtain in the United States, but such information is available in Denmark through the Danish Abortion Register, Birth Register, and Population Register.

Investigators at the University of Southern California are conducting a study to prepare a catalog of statistical information on childlessness and one-child fertility found around the world. A comparative analysis of data from the United States and a variety of other countries is being made, using demographic and social variables.

A grant to the East-West Center in Hawaii is exploring trends and differentials in the timing of births using data from two national surveys of Korea and the Philippines. The purpose of the study is to describe and analyze the socioeconomic and cultural determinants of child spacing in two economically developing countries.

Investigators at Cornell University are involved in a 2-year study to examine the differences and similarities of the effects of community variables and individual family characteristics on fertility and mortality in Costa Rica, El Salvador, Guatemala, Honduras, and Nicaragua. The project will analyze economic factors in fertility decision-making and in infant and child mortality, relating all these factors to demographic transition in Central America.

A 2-year grant to the University of Michigan supports a study on fertility and family planning in Taiwan. The project is examining continuities and changes in the relationship between measures of modernization and fertility at the macro level, and changes in attitudes affecting reproductive behavior at the individual level.

Investigators at Northwestern University are conducting studies on the causes and consequences of high-level migration from the Philippines to the United States. In recent years, the Philippines has been the single largest contributor of professional and technical worker-immigrants to the United States. The study will examine trends in migration from the viewpoint of the individual.

A grant to the Massachusetts Institute of Technology is assessing the impact of government policies and programs on out-migration from rural communities in developing countries, using Mexico as a case study. Investigators are examining interrelationships between internal and international migratory movements by identifying the social, economic, and political consequences of Mexican migration to the United States, both legal and illegal.

In addition to the contracts and grants research program, the CPR has established a collaborative working relationship with the U.S. Agency for International Development (AID) and the World Health Organization (WHO). This involves convening meetings for sharing program information and plans, exchange of progress reports, and staff

consultations; providing testing for long-acting drugs that have been synthesized by WHO contractors; and supporting joint studies.

The director of CPR chairs the Interagency Committee on Population Research that coordinates population research activities supported by Federal agencies and fosters the exchange of information among the member agencies.

Center for Research on Mothers and Children (CRMC)

During FY 1978, the CRMC engaged in 11 international research projects, summarized below by program area.

Human Learning and Behavior Branch (HLBB)

The NICHD supports a series of cross-language studies comparing the processes that underlie the reading of English and Serbo-Croatian, the language of Yugoslavia. The research is designed to increase our understanding of how the processes of reading interrelate with the language system that a person has at the time reading is acquired. This research has been conducted in close collaboration with New Haven, Connecticut, based American scientists who are also supported by the NICHD.

This study and others conducted in Yugoslavia were recently reported at a cross-language conference held at NIH and sponsored by the NICHD and the Fogarty International Center.

Pregnancy and Infancy Branch (PI)

The PI Branch of CRMC supported 10 international research projects.

Investigators at the University of Melbourne, Australia, conducted chemical studies of relaxin and its receptors to delineate the many aspects of the chemistry and biological reactivity of the hormone relaxin, which has recently been purified. Studies on the amino acid sequence of the various forms of porcine relaxin found in pregnant porcine ovaries, as well as the sequence of prorelaxin, were conducted.

A grant to Murdoch University, Australia, supported studies on delayed implantation and development in marsupials. Studies were conducted to determine the role of uterine secretions and extrauterine substances, especially hormones, in the initiation and maintenance of fetal development; and the correlation of the phases of embryogenesis with the metabolism of the embryo, especially in relationship to embryonic diapause and subsequent reactivation of the embryo.

Investigators at the University of Bristol, England, conducted studies on the control of breathing before and after birth. Mature

exteriorized sheep fetuses were studied to identify the level and type of central inhibition that renders respiratory and nonspecific stimuli ineffective. They also hoped to identify the principal drive to ventilation in the fetuses.

A grant to McGill University, Canada, supported studies on formation, metabolism, and the role of hormones in pregnancy. This project studied the mechanisms that control heme synthesis in human fetal liver by cell culture techniques. It also investigates the factors that are responsible for the induction of surfactant formation in fetal lung.

Investigators at the University of Manitoba, Canada, examined membrane receptors for placental lactogens of several different species, PRL, GH, and insulin. The major thrust was to illuminate the dynamic state of receptors in target tissues and to establish more fully the importance of receptors in hormone action.

A grant to the Baker Medical Research Institute, Australia, examined respiratory system development and sudden infant death. This study was conducted to elucidate the chemical and neural control of the respiratory system of fetal lambs in utero, during birth, and in the immediate postnatal period, and the influence of respiratory activity and lung liquid flow on the maturation of the respiratory system.

Investigators at the University of Toronto, Canada, conducted a correlated neurophysiological and morphological study of neuronal mechanisms possibly involved in or causative of the sudden infant death syndrome.

A grant to the University of Edinburgh, Scotland, supported the study of genetic analysis of embryonic limb growth in mice. Investigators attempted to pin down more precisely the differences between high body weight and low body weight lines of mice that have been produced by artificial selection. The study examined limb growth parameters in mice that were selected for large and small body size in the hope of identifying physiological correlates of genetic differences in growth rate.

Investigators at the University of Trondheim, Norway, conducted studies on the effects of maternal age, parity, marital status, and spacing of births on the survival of births within different sibship sizes. In addition, the investigators made a comparison of the causes of infant death in Norway and in selected U.S. states.

A grant to the University of Oxford, England, supported the development of animal models for studies of SIDS. Pursuing the lead that the apnea may be triggered in young lambs by certain liquids such as water, cow's milk, or human milk, the investigators discovered that two types of mucosal water-sensitive units were found in the superior laryngeal nerves. These two types of mucosal units were found also in cats and Rhesus monkeys at each stage of maturity. The investigators found that slowness of heart beat and hypertension appear to be chiefly mediated via pathways other than the superior laryngeal nerves.

In FY 1978 the DNB Branch supported six international research studies that are summarized below.

Investigators at Johns Hopkins University are conducting studies on the role of staple food in infant nutrition. One project is studying groups of children in Peru to determine how well certain locally available staple foods (potatoes, wheat) satisfy the energy and protein needs of infants with diverse nutritional requirements.

A grant to the Medical College of Wisconsin supported work on malnutrition and development of physical fitness in children. A group of males ages 6-16 are being studied in Cali, Colombia, to determine their work capacity and nutritional status. The three groups studied represented high socioeconomic urban, low socioeconomic urban, and low socioeconomic rural children. This study will provide a quantitative assessment of the influence of poor nutritional history on the development of physical work capacity, and an excellent opportunity to learn the impact of urban life on the growth and development of children.

Investigators at the University of California at Los Angeles conducted a study at Nairobi, Kenya, on the relationship of early malnutrition, immunologic competence, and immunity to measles. In this project 75 mother-infant pairs in which the baby suffered intrauterine growth retardation and 75 control pairs are being studied to determine the immunologic and nutritional correlates of varying degrees of intrauterine malnutrition, and the incidence, causes, and consequences of measles vaccine failure. Preliminary results show decreased cellular immunity, not only in the group of infants weighing less than 2,500 grams at birth, but also in the group weighing 2,501 to 2,800 grams.

A grant to the Harvard School of Public Health, involving a collaborative effort with the University of Giessen (Germany) and the Nutrition Division of the Colombian Institute of Family Welfare, supports a study on malnutrition and its effects on psychological development in Bogota, Colombia. This study examines the effects of environmental deprivation and malnutrition in late pregnancy and during the first 3 years of life on physical development, psychomotor functions, and cognitive development. Results indicate that the nutritional supplement provided was associated with increments in weight gain during the last trimester of pregnancy and in birthweight of male babies. The supplemental program was also associated with a decrease in the rate of stillbirths and neonatal and perinatal mortality. During the first 18 months of life, the supplementation resulted in significant increments in the rate of weight and height gains. Improvement in locomotor and cognitive measurements were obtained in a stimulated group of children.

Investigators at the Medical University of South Carolina conducted a study on genetic childhood diseases and aging, for the purpose of determining immunologic approaches to the detection of disease. In one subproject, antibodies to human cartilage were detected in the serum of leprosy patients from two different geographic areas of Papua,

New Guinea. As yet, it is not clear to what extent these antibodies are implicated either in the pathogenesis or the complications of leprosy or in the prolongation and intensification of inflammatory reactions involving collagen at sites such as the skin, nerves, and glomerular basement membrane.

A grant to the Medical College of Virginia supported a major study in human genetics using panels of twins to investigate genetic components of diseases, behaviors, and twinning. A previous study of Danish twins by the principal investigator showed that a female twin exposed to a male twin in the uterus had a higher risk of developing ovarian cancer. The researchers expanded that analysis, using a large tumor registry at the Medical College of Virginia. A Norwegian Twin Registry will also be used to define genetic, maternal, and environmental factors in the production of fetal wastage and congenital defects. An attempt will be made to assess genetic components as well as environmental components by comparison of families of twin mothers with families of twin fathers.

Mental Retardation and Developmental Disabilities Branch (MRDD)

During the reporting period the MRDD Branch engaged in 3 international research projects that are summarized below.

A grant to the New York Blood Center is supporting a 5-year research program in cytogenetics involving correlations of karyotype and phenotype on patients. The laboratory has facilities available for training of visiting scientists from abroad in the area of cytogenetics.

A 5-year grant to Albert Einstein College of Medicine supports a study to examine the socialization of young people who have different types of mental retardation, with particular emphasis on the transition from childhood to adulthood. The present study uses a defined population of retarded subjects studied in Aberdeen, Scotland, 10 years ago. The results of this study will aid in understanding the problems encountered by older mentally retarded individuals in adapting to society, and the socialization processes that enhance or detract from later life adjustment.

An extension of a study initiated by the Youth Aliyah, Jerusalem, Israel, on cognitive functions of retarded early adolescents is being conducted in the United States through Institute support of MR research centers. This research activity will contribute knowledge on educational interventions that can be introduced to prevent or reverse cognitive impairment resulting from depriving life experiences.

Intramural Research Program (IRP)

During the reporting period, the IRP also participated in international research activities. The NICHD, under the authority of the U.S.-Polish Bilateral Health Agreement, entered into a collaborative

research agreement with the National Institute of Mother and Child, Warsaw, Poland. Three Polish scientists visited the NICHD to undertake collaborative research activities. Dr. K. Mataszeuiska and Dr. A. Pickarczyk worked with Dr. Philip Nelson in the Laboratory of Developmental Neurobiology; and Dr. A. Sito worked at the Moore Clinic at Johns Hopkins University investigating clinical genetics. Dr. Philip Nelson, NICHD, traveled to the National Institute of Mother and Child, Warsaw, Poland, to undertake collaborative research activities.

Director's Activities

The Director of the Institute participated in "Priorities in Manpower for Child Health Services in Developing Countries," a workshop sponsored by the 15th Congress of the International Pediatric Association (IPA) in New Delhi, India. He served on the Executive Committee of the IPA, as well.

The Director served as a consultant to the Division of Family, Maternal, and Child Health of the World Health Organization (WHO). The division meeting was held in Geneva, Switzerland, June 15-18, 1978.

A publication from an earlier Congress of the International Organization for the Study of Human Development (IOSHD) appeared during FY 1978: *Mutations: Biology and Society* edited by Dwain N. Walcher, Norman Kretchmer, and Henry L. Barnett.

The Director of the Institute, who serves as chief of the Developmental Gastroenterology and Nutrition Section, Intramural Pregnancy and Infancy Research Branch, initiated an exchange program to bring two foreign fellows to the NICHD. They are Dr. Shimon Walter Moses, Faculty of Health Sciences, Ben-Gurion University of Negev, Beersheba, Israel, and Dr. Francis D. Raul, National Institutes of Health in France.

Institute Trends in International Activities and Proposed New Directions

It is the intent of the NICHD to continue to support international research activities to investigate health problems that are in concert with the mission of the Institute — to improve the health and well-being of mothers and children. Many of the problems associated with pregnancy, infancy, and childhood overlap geographic boundaries. Solutions to these problems may be found in collaborative research activities between scientists involved in similar investigative research, both nationally and internationally. As new ties are initiated with developing countries, the Institute hopes to engage in an exchange of scientific information to facilitate the acquisition of new knowledge. Our awareness of shared world health problems has led us to conclude that there is a critical

need for an expansion of international research activities aimed at ameliorating and/or preventing morbidity or mortality. These efforts would serve to strengthen and enhance the quality of life for all.

National Institute of Dental Research

The National Institute of Dental Research continues to engage in, and actively support, international scientific collaboration and contacts directed toward the common global goal of dental disease prevention and control.

Emphasis has been placed on Institute staff participation in, and financial support of, international meetings and the publication of their proceedings, the funding of foreign grants, and provision of research opportunities for visiting scientists. These endeavors result in mutual benefits leading to the advancement of dental research knowledge and have enabled individual scientists to make a personal contribution to international dental public health.

During FY 1978, the National Institute of Dental Research financially supported three international meetings:

Tenth International Biomaterials Symposium
Second World Congress on Pain
International Association for the Study of Pain and Satellite
Conference on Oral-Facial Pain

Institute staff members presented research reports, chaired scientific sessions, served as committee members, or participated as discussion panelists at 35 international meetings listed below.

13th International Congress of Genetics
6th European Teratology Society Congress
13th International Embryological Congress
International Conference on Electrolyte Precipitation in
Aqueous Solutions
International Symposium in Pediatric Stomatology
11th International Congress on Nutrition
European Federation of Connective Tissue
International Congress for Microbiology
2nd World Congress on Pain
7th International Biophysics Congress
6th International Conference on Magnetic Resonance
International Symposium on New Dentifrices
Federation Dentaire Internationale

14th Annual Meeting of European Associations for the Study
 of Diabetes
 International Symposium on Collagenase in Normal and
 Pathological Connective Tissues
 Symposium on Studies in Joint Disease
 4th European Immunology Congress
 Norwegian Section, Scandinavian Society of Pedodontics
 Symposium on Pathobiology of Viral Diseases
 7th International Congress of Reticuloendothelial Society
 12th Leukocyte Culture Conference
 International Conference on Periodontal Research
 European Organization for Caries Research
 Pan American Health Organization
 3rd International Workshop on Calcified Tissues
 South American Biochemical Congress
 World Health Conference on Periodontal Diseases
 International Sociological Association
 Scottish Health Association
 10th International Biomaterials Symposium
 International Association for the Study of Pain and Satellite
 Conference on Oral-Facial Pain
 Australian Division of the International Association of Dental
 Research

The Institute funded six foreign research projects, one research fellowship, and one contract, covering the areas of craniofacial anomalies, periodontal disease, dental caries, and soft tissue stomatology.

Within the Intramural Programs of the Institute, 44 international scientists were invited to present seminars on dental research topics. Six visiting associates, 6 visiting scientists, 15 visiting fellows, and 21 guest workers conducted research studies within the Bethesda laboratories of the Institute.

Fluorine in Stomatology and Hygiene, a compendium of information for use by health professionals, was translated from Russian and published during the year. This 1,000-page reference volume was distributed to selected individuals and libraries throughout the world.

NIDR Abstracts, the quarterly publication containing summaries of scientific reports published by NIDR investigators, is distributed to approximately 150 foreign colleagues.

In cooperation with the Smithsonian Science Information Exchange, the NIDR annually publishes *Dental Research in the United States and Other Countries*. Dental scientists around the world are urged to register their research projects in this exchange of dental research information.

The Director, NIDR, continued to serve as a member of the Oral Health Research Advisory Group of the Oral Health Unit, World Health Organization.

National Institute of Environmental Health Sciences

Introduction

The 12 years that NIEHS has been in existence have brought enormous changes in the field of environmental health. The cross-cutting and pervasive nature of the problems in this field have fostered extensive cooperation and collaboration at the international level, with institutions and with individual scientists. Our knowledge base has increased, as has awareness in the scientific and public arenas; even so, issues of environmental health science remain complex.

Against this backdrop of continuing legislative, executive, and public interest the NIEHS carries out its mission of providing the scientific information base, advanced scientific methodology, and trained scientific manpower to reach an understanding of the total impact of environmental factors on human health. International collaboration is an important facet of this program.

Scientists at the NIEHS will continue to use all available avenues to make the world a safe place in which all peoples may work and live.

U.S.-U.S.S.R. Cooperation

Collaboration between Soviet and American environmental health scientists is carried out under the auspices of two cooperative agreements between the United States and the Soviet Union. Under the Medical Science and Public Health Cooperative Agreement, scientists from both countries are conducting joint research on heart disease, cancer, arthritis, influenza and acute respiratory diseases, and on health problems associated with environmental pollution. The Director, NIEHS, is U.S. Coordinator for the environmental health activities under the Health Agreement.

FY 1978 was the sixth year of formal collaboration between the U.S. and U.S.S.R. in environmental health research. The first year was concerned largely with establishing working relationships and agreeing on areas of joint study. Cooperative research efforts initiated in the second year of the agreement involved exchange visits between scientists of both sides. The research results developed during the second and third years of collaboration were presented by American and Soviet scientists at a joint symposium in Riga, Latvia, in December 1974. Scientific results from cooperative research during 1975 and 1976 were presented at the second joint symposium, held in Marineland, Florida, in December, 1976. The results of these symposia were published in both countries. During 1977 and 1978, major workshops were held on the topic "Embryotoxic and Teratogenic Effects of Chemicals" (Leningrad, November, 1977); and "Biological Effects of Metals" (Cincinnati, February, 1978).

Collaborative research efforts are currently divided into four problem areas aimed at (1) developing methods for the quantitative evaluation of the biological effects of environmental chemical agents; (2) predicting the biological effects of environmental chemical agents; (3) studying the long-term biological effects of environmental chemical agents; and (4) studying the long-term effects of physical factors in the environment.

By the end of 1978, over 50 scientific papers will have been published by American and Soviet scientists on the results of environmental health research conducted under this agreement.

The Agreement on Cooperation in the Field of Environmental Protection between the U.S. and U.S.S.R. addresses some of the most important aspects of problems of the environment, including the study of pollution and its effects on life. A number of agencies participate in this agreement, which is under the general direction of the Administrator, EPA. The Director, NIEHS, serves as HEW representative to the agreement and as co-chairman of the working group for one of its areas, the Biological and Genetic Effects of Pollutants. Effort in this area has been focused on the mutagenic potential of environmental contaminants, the toxic effects of heavy metals in the environment, environmental health hazards associated with extraction, processing and utilization of oil from shale, the effects of environmental pollution on the neuroendocrine system with special emphasis on human behavioral effects, and the use of marine organisms to study the biological and genetic effects of pollutants and as models for biomedical problems.

During 1978, program activity under this agreement consisted of the fourth joint workshop on "Basic and Practical Approaches to Environmental Mutagenesis and Carcinogenesis" held in Baku, U.S.S.R., and participation in the joint workshop on the topic "Biological Effects of Metals," held in Cincinnati, Ohio. In addition, exchange visits took place on the topics of health effects of oil shale development, human behavioral effects, and marine organisms.

U.S.-Japan Cooperative Medical Sciences Program

The Joint Panel on Environmental Mutagenesis and Carcinogenesis organized a Conference on Modification of Mutagenic and Carcinogenic Activity, which was held in October 1977. A wide range of genetic, biochemical, and environmental modifying factors were discussed. It was clear from the presentations that mutagenic response can be markedly modified, quantitatively as well as qualitatively.

The Seventh Joint Conference held under this program was held in July 1978 at Lake Yamanaka and dealt with the Utility of Sister-Chromatid Exchange. A 5-year review of the work on the U.S.-Japanese Panel followed this workshop.

U.S.-Egypt Cooperation

Under the auspices of the U.S.-Egypt Joint Working Group on Medical Cooperation, the National Institute of Environmental Health Sciences has been responsible for staffing and guiding the U.S. activities of the Subcommittee on Environmental Health. In June 1978, the U.S. Subcommittee visited Cairo and met with the counterpart Egyptian Subcommittee. At that same time the full Joint Working Group developed and approved a program of specific research and methodology development projects.

This program has emphasized the development within Egypt of the capability to effectively monitor the environmental levels of known toxic agents in industrial and agricultural settings, and to assess at the policy level the effect of growing agricultural and industrial pollution within the specific ecology and environment of Egypt.

Implementation of this program has been delayed by a reconsideration of program priorities in the light of limitations on available P.L.-480 funds to support research and development activities in Egypt. Plans for 1979 will be reevaluated by the Environmental Health Subcommittee, and a revised program of projects will be resubmitted to the Joint Working Group in June 1979.

Collaboration With the World Health Organization

NIEHS is a World Health Organization collaborating center for environmental health. NIEHS staff have been deeply involved in support of WHO programs.

Specifically, staff have been involved with the preparation of a World Health Organization-sponsored document on "Environmental Health Problems Associated with the Manufacture of Synthetic Organic Chemicals"; participated in a meeting to help implement World Health Organization Assembly Resolution 30.47 on a new approach regarding the international evaluation of the effects of chemicals on health; and attended a WHO-EURO meeting dealing with the health consequences of chemicals occurring naturally in drinking water. In addition, one of our scientists served as chairman of the scientific advisory committee to the International Register of Potentially Toxic Chemicals of the United Environmental Program.

In December 1977 Dr. Stephen Brown participated in a PAHO Workshop on Environmental Epidemiology in Mexico City.

Also in December 1977, Dr. Warren Piver traveled to Geneva to participate in a UNEP meeting on Chemical Industry.

During the month of October 1977 Dr. Bruce Fowler traveled to Stockholm, Sweden, to serve as a temporary advisor to WHO and participated in a meeting to review biomedical parts of the draft criteria document on arsenic.

Dr. Robert Dixon traveled to Buenos Aires and Santiago in July 1978 to participate in a site visit to the South American WHO Collaborating Center for Research and Training in Human Reproduction in order to review their ongoing research projects and training activities.

In June 1978 the International Agency for Research on Cancer convened a working group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans to consider some halogenated hydrocarbons and prepare background data on specific compounds. Dr. John Moore was invited to come to Lyon for this meeting because of his expertise in this field.

Drs. Richard Bates and Joseph Haseman traveled to Hanover, Germany, in May 1978 to attend the organizing committee meeting of the IARC Working Group to establish basic requirements for carrying out long-term and short-term carcinogenicity and related tests.

The Joint IARC/NIEHS Working Group on the Coordination of Epidemiological Studies on the Long-term Hazards of Chlorinated Dihenzodioxins and Chlorinated Dihenzofurans met in Lyon, France, in January 1978. Dr. John Moore was the NIEHS expert at this meeting.

Dr. David Rall traveled to Lyon, France, at the request of IARC, to present recommendations on the criteria for evaluating the carcinogenic risk of chemicals to man and to serve as a member of the panel, which reviewed the papers to be presented at the Symposium on Carcinogenic Risks-Strategies for Intervention.

In November Dr. Robert Dixon served as a temporary advisor to the Fourth Toxicology Review Panel of the WHO Special Programme of Research, Development, and Research Training in Human Reproduction.

In December Dr. T.M. Ong was asked to give a presentation at a training course in Methods for Detection of Environmental Mutagens and Carcinogens for scientists in Central and South America. The meeting was held in Mexico City.

In October the WHO Toxicology Review Panel invited Dr. E.E. McConnell to visit the Institute Latin American de Fisiologia de la Reproduccion in Buenos Aires to assess the potential of that group to carry out programs in acute and subacute toxicology. The discussions centered around preclinical safety evaluations of potential therapeutic agents.

Also during this month, Dr. David Hoel traveled to Lyon, France, to participate in a meeting of the Working Group on Criteria for Evaluating the Carcinogenic Risk of Chemicals to Man.

Other International Collaboration

NIEHS has a contract with the University of British Columbia, Vancouver, British Columbia, to assay environmental chemicals for mutagenic activity in a meiotic non-disjunction test in *Neurospora crassa*.

In order to develop a truly comprehensive battery of tests for mass screening programs, we must be able to detect all classes of genetic alterations. No such assay exists for non-disjunction. Because of this, we have only scanty evidence of chemicals which will cause non-disjunction. The assays with *Neurospora* have detected activity in 10 chemicals out of 62 tested. This is an important class of genetic alternation with regard to genetic disease in man.

Because of the marked specificity of some chemical mutagens, it is considered essential to continue work with the *Neurospora* assay to evaluate its utility and feasibility as an assay system in mass screening programs.

NIEHS has a grant with the State University of Leiden, Leiden, the Netherlands, to study induction of genetic damage by chemical mutagens. It is proposed to undertake a systematic study of the frequencies with which different categories of genetic damage are induced in a variety of different germ cell stages by representatives of both directly and indirectly acting mutagens under modifying conditions, such as storage. In addition, it is proposed to investigate in model populations the induction of genetic damage at physiological relevant concentrations after chronic application versus short-term exposure.

NIEHS supports a grant at the University of Western Ontario, London, Canada, to study the nature of lead and mercury binding nuclear proteins. The major objectives of the study are to determine the nature of proteins forming intracellular complexes with potentially toxic metals (lead and mercury), the functional changes in the cell containing intranuclear inclusions and the effect of chelating agents in tissue culture to remove the metal. These metals are known to bind intracellularly with acidic nuclear proteins, but it is not known whether these proteins are synthesized specifically for binding with these metals.

Another grant with the University of Turku, Turku, Finland, has investigators studying gastrointestinal and pulmonary metabolic functions. It is well accepted that the gastrointestinal tract actively participates in foreign substance metabolism. Recently similar activities have been demonstrated in pulmonary tissue. Further exploration of these functions is planned. Further identification of the biochemical machinery carrying out these numerous functions will be attempted. In addition, adaptation of these functions on subcellular levels under various experimental conditions will be studied.

NIEHS supports a grant to TelAviv University, Ramat Aviv, Israel, to study hydrocarbon recognition in petroleum-degrading bacteria. Research is being carried out on the transport of water-immiscible and water-soluble petroleum hydrocarbons by microorganisms. Emphasis is on characterization of bacterial emulsifying agents and their role in hydrocarbon movement from the medium to the cell surface and across the cell membrane.

Dr. I.P. Lee and scientists from the Institute of Toxicology and the University of Zurich are collaborating on developing a new method for accurately identifying mutagens and carcinogens through an in vivo animal model.

The MRC/ICI/NIEHS international trial to test paired compounds consisting of chemical carcinogens and noncarcinogenic structural analogs as well as selected chemicals to serve as positive and negative controls has been continued. This study has been developed in cooperation with the Medical Research Council and the Imperial Chemical Industries in Great Britain, the International Association of Environmental Mutagen Societies and NIEHS. The study will involve collaboration between 50 scientists in different laboratories all over the world who will compare various assays for mutagenicity in blind tests on about 42 compounds.

A collaborative study on the effects of inhaled asbestos was begun with the Pneumoconiosis Research Unit, Medical Research Council, United Kingdom. Using an agreed upon protocol, we are studying the respiratory effects of various types of fibers which may be present in either the working environment or the rest of our environment. Major concentration is on asbestos but we are also looking at glasswool and rockwool.

Collaborative research between the Transplacental Toxicology Workgroup at NIEHS and Dr. Manfred Metzler, Institute for Pharmacology and Toxicology, University of Wurzburg, Wurzburg, West Germany, includes studies on the target organ metabolism and bioactivation of the carcinogenic estrogen, diethylstilbestrol (DES). These studies involve whole animal experiments and tissue culture systems as well as studies on the in vitro binding of DES or its metabolites to intracellular and extracellular receptor proteins. Such studies should provide new insights into mechanisms of hormonal carcinogenesis.

Collaborative work on the effect of hormones and hormonally active xenobiotics on the control of blood coagulation in the rat has been and is now being done with Dr. Etsuko Kita, Department of Clinico-Laboratory Diagnostics, Nara Medical College, Nara, Japan, and Dr. Coral Lamartiniere of NIEHS. In addition, Dr. Kita was a guest worker in Dr. Lamartiniere's lab during the period May 1977 to May 1978.

During the past year we have continued to support the Environmental Mutagen Information Center by interagency agreement at the Oak Ridge National Laboratory. The Center continues to work closely with investigators around the world in both obtaining and supplying information on the subject of environmental mutagenesis. The Center has over 25,000 bibliographic entries in its data banks and continues as a unique worldwide resource for information in the area of environmental chemical mutagenesis.

Communication of basic and applied information vital to environmental health problems is aided by establishing mechanisms for information exchange. In this regard, NIEHS has established the much-needed Environmental Teratology Information Center in collaboration with the Department of Energy and the Oak Ridge National Laboratories. Information on teratology is collected, indexed and made available to the biomedical community directly from the Center or the National Library

of Medicine's TOXLINE. ETIC is a unique worldwide resource for information in the area of teratology.

Professor F. Pocchiari and Dr. L. Giannico, Ministry of Health, Rome, met with NIEHS scientists to discuss "Health Aspects of Environmental Pollution." The following areas were agreed upon for cooperation:

- A. Evaluation of chemicals for possible human toxicity
 - 1. Chemical selection
 - 2. Test methodology
 - 3. Extrapolation of results from laboratory animals to human populations
 - 4. Assessment of risks to the human population
- B. Understanding the mechanism of action of environmental chemicals with possible human toxicity
- C. Surveillance and epidemiological assessment of the effects of environmental chemicals in human and nonhuman populations

National Institute of Neurological and Communicative Disorders and Stroke

Introduction

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) serves as the NIH focal point for research on the basic and clinical aspects of the nervous system and human communication. Through its research grant program, participation in the Special Foreign Currency Program and collaborative research efforts between NINCDS scientists and their foreign colleagues, the Institute maintains a continuing interaction with neurological and communicative scientists internationally.

In addition, since 1975 the NINCDS has been one of eight WHO Collaborating Centers in the Neurosciences. These centers, positioned strategically throughout the world, further international research efforts on neurological disorders, and initiate and demonstrate community programs for the prevention and treatment of such disorders. At this time, special emphasis is being given to the cerebrovascular disorders (stroke) and the convulsive disorders (epilepsy).

As part of this effort, the NINCDS, the Fogarty International Center, and WHO jointly sponsor a Neuroscience Fellowship Program. This program provides men and women from developing countries with stipend support for advanced training in the United States, to prepare them for academic and public health careers in their own countries.

Foreign Research Grants

NINCDS supported 13 foreign research projects in FY 1978, totaling \$1,082,905. Four of these projects were in Canada; three in Israel; two in Sweden; two in Mexico; one in Italy; and one in New Zealand. These grants represent both clinical and basic research, and have been awarded to outstanding investigators exploring problems of high priority to the United States and their own countries. The largest award is to Henry J. Barnett of the University of Western Ontario (\$645,811) for an international multi-institutional cooperative study evaluating the efficacy of extracranial/intracranial arterial anastomosis.

Foreign NINCDS research grants complement those made to U.S. investigators in that they are expected to provide information not being adequately developed in this country. In some cases opportunities are unique to the country involved; in all cases the workers are outstanding and their contributions will help American scientific efforts. They are an important aspect of international health cooperation; they place NIH financial and intellectual resources in contact with the skills, opportunities, and resources available in other countries. The entire process of accumulation of knowledge in the neurosciences is thus materially enhanced.

Special Foreign Currency Program (P.L.-480) Grants

NINCDS currently sponsors 11 P.L.-480 projects: three in Egypt; one in India; three in Poland, and four in Yugoslavia. FY 1978 funding was for the three projects in Egypt, totaling \$338,691. These were a project for perinatal screening of developmental malformations, and two studies of the biochemistry and enzymology of poisonous snake venoms affecting the nervous system.

P.L.-480 grants are a small but important segment of the NINCDS-NIH research support program in that they provide information not being adequately developed here. In some cases, opportunities are unique to the country involved; in others, special economies are possible through this program. In all cases the investigators are outstanding and their contributions will help to advance the world's knowledge in the neurosciences.

WHO Collaborating Centers for Research and Training in the Neurosciences

NINCDS is one of eight WHO Collaborating Centers for Research and Training in the Neurosciences. The others are:

The Instituto Nacional de Neurologica; Mexico City, Mexico
The Montreal Neurological Institute; Montreal, Canada
The Groupe Hospitalier de la Timone, Marseilles, France
The Centre National de la Recherche Scientifique; Strasbourg,
France
The University of Geneva; Geneva, Switzerland
The University of Ibadan; Ibadan, Nigeria
The Academy of Medical Sciences of the U.S.S.R.; Moscow,
U.S.S.R.

Each center funds its own activities, which consist of collaborative research, publications for scientific information exchange, support of conferences and courses, advisory services, and training. In FY 1978, Drs. Donald B. Tower and Murray Goldstein of NINCDS presented lectures as part of a Collaborating Centers Program-sponsored training course in cerebrovascular disorders and stroke in Lima, Peru.

In FY 1978, NINCDS funding for this activity was limited to program travel expenses. Funds have been set aside to support international research fellowships in 1979 in the amount of \$100,000.

This program meshes with the broader commitments of NIH for international health cooperation. Opportunities for neuroscience collaboration and interchange with scientists in other countries are virtually unlimited. Stroke epidemiology is a good example of an area where great mutual benefits are possible, as there are known to be wide variations in stroke mortality, incidence, and age groups affected in different parts of the world.

The principal aspect of this program, in relation to international health cooperation, is that it brings together the world's experts in the various neuroscience areas so that their combined knowledge is brought to bear on problems common to all countries.

This program was begun in 1974 with five centers, and has since been expanded to eight. Major emphasis is now on stroke and epilepsy, two problems severely affecting health in every country of the world. In terms of time, the program is ongoing, and will continue as funds and staff resources permit.

The trend in NINCDS foreign research grants has been downward because of the increased competition for funds and the leveling off of appropriations in real dollar terms. The Institute hopes to maintain the level of funding for these grants, but this will depend upon future economic and budget factors.

The trend in P.L.-480 research grants has been downward, because of decreased availability of counterpart funds in the countries where neuroscience research can be conducted.

Interest in the Collaborating Centers Program is growing, and activities are steadily increasing. The Institute hopes to be able to continue to cooperate and contribute as it has in the past.

National Library of Medicine

The National Library of Medicine (NLM) is a national resource with international impact. Its international activities include: bilateral quid pro quo MEDLARS agreements; exchange of biomedical literature; collaboration with national and international organizations in their establishment of regional services; information services to the developing countries through an NLM/Agency for International Development (AID) agreement; special foreign currency program for the support of publications; participation in international organizations; providing technical consultation; and receiving non-U.S. colleagues for specialized training.

International MEDLARS Agreements

NLM has 11 international MEDLARS partners: Australia, Canada, France, Germany, Iran, Japan, Mexico, South Africa, Sweden, United Kingdom, and the Pan American Health Organization (PAHO). Policy officials and directors of the foreign MEDLARS centers attended the Fifth Meeting of the International MEDLARS Policy Advisory Group October 27-28, 1977. This meeting provided an opportunity for joint review of policies, experiences and future plans of NLM and the centers.

At the meeting, issue papers were presented on document delivery by Sir Harry Hookway and Dr. Philip Holmes of the United Kingdom; data base building by Dr. Henry Kissman, NLM associate director for Specialized Information Services; and networking by Dr. S. Abrahamsson and Dr. Goran Falkenberg of Stockholm, Sweden.

Of particular interest were the regional activities of the Pan American Health Organization's Regional Library of Medicine (BIREME) and the Pahlavi Library of Medicine in Iran which was designated in 1978 as the WHO Regional Library for the eastern Mediterranean. One principal concern of the policy group was how to provide services to the developing countries now that WHO has terminated its MEDLINE activities. Most of the centers are faced with limitations on personnel, and extensive free services to the developing countries could be undertaken only if sponsored and funded by the appropriate technical assistance or development agency within the providing countries.

The quid pro quo bilateral agreement, which is the basis for international MEDLARS collaboration, continues as an effective mechanism for cooperation. Together, these bilateral arrangements constitute essentially an international network in which the value of biomedical information is recognized as vital to the advancement of medical research, education, and the improvement of health. Table 1 summarizes the modes of access to the NLM data bases. Ten data bases—MEDLINE, TOXLINE, CHEMLINE, CATLINE, SERLINE, AVLINE, CANCERLIT, CANCERPROJ, CLINPROT, RTECS—are available to the foreign centers, but not all centers have chosen to search all data bases.

Table 1. International Access to MEDLARS

Tapes	Tapes/Software	Online NLM
Germany ⁺	Sweden ⁺	France
Japan	United Kingdom ⁺	Canada
	Australia ⁺	Iran
	PAHO	Mexico
		South Africa

⁺ Supplemental online access to NLM computer

International Exchanges and Services

The NLM continues its international publications exchange program with 810 institutions in 87 countries where an equitable exchange balance can be achieved. This program is in addition to NLM's regular acquisitions program and often provides both NLM and the participating country with material not easily obtained otherwise.

In FY 1978 the assistant director for International Programs was invited to visit Cuba by the Minister of Public Health to observe Cuba's health information activities. As a result of this visit, a cooperative program was established in the exchange of publications between the National Information Center for Medical Sciences of the Ministry of Health in Cuba and NLM. The Library also accepted for special training Pompeya Garcia, director of the National Medical Library of Cuba and Diasy de Valle, director, Department of Information Development of the National Information Center for Medical Sciences.

The NLM provides interlibrary loans of published and audiovisual materials internationally for a fee. Exceptions have been made for countries with which the United States Agency for International Development has a health program. Under an agreement between AID and NLM, the Library has provided during the past year approximately 22,000 interlibrary loans, 12 reference replies, 497 MEDLINE searches, 52 subscriptions to *Index Medicus* and 48 subscriptions to *Abridged Index Medicus*. Approximately 25 percent of these were for technical support of PAHO's Regional Library of Medicine in Sao Paulo, Brazil; 36 percent to Turkey; 10 percent to India; 9 percent to Indonesia; and 7 percent to Korea. This agreement terminates at the end of FY 1978. Future international interlibrary loan of documents and loan of audiovisual material will be on a fee for services basis only.

Special Foreign Currency Program

The Library's Special Foreign Currency Program, authorized by Public Law 83-480, made 20 new awards in FY 1978 for a total of 88

active projects for \$1,680,423 (equivalent). Under the NLM SFC program, appropriations of U.S.-owned, local foreign currencies are utilized for scientific writing projects in cooperating countries, including Poland, Tunisia, India, Pakistan, Egypt, and Yugoslavia. The collaborative NLM program also is continued in Israel through a bloc award from the U.S.-Israel Binational Science Foundation.

Included among the projects in the seven cooperating countries are the preparation of critical reviews and monographs analyzing biomedical research and practice; translations of foreign monographs in the health sciences; studies in the history of medicine; the publication of major international symposia and conference proceedings; and the preparation and publication of authoritative bibliographies, guides, and other literature tools in the biomedical sciences. The program makes it possible for the Library to procure and disseminate published information which is important to the progress of the biomedical sciences and the public health, using foreign scientific personnel and resources.

Critical reviews and biomedical monographs continue to be the most frequent type of project undertaken in the program, constituting 66 percent of the funding. Fifty-five percent of all projects active in FY 1978 were undertaken in two countries—Poland and Israel. During FY 1978 Dr. Saul Jarcho, consultant to the NLM Board of Regents, accompanied by Dr. Jeanne Brand, chief of NLM's International Programs Division, carried out a program review of the Library's publication activities in Egypt. Among other projects currently being developed in that country are a series of studies in the history of Arabic medicine.

Examples of new projects activated in FY 1978 include a critical review on surgery of the spleen, a translation of a Russian study of emotional stress and arterial hypertension, and a catalogue of manuscripts on medicine and pharmacy in the National Library of Cairo and the Municipal Library of Alexandria, Egypt.

Among the books published in FY 1978 under this program was *Early Therapeutic, Social and Vocational Problems in the Rehabilitation of Persons with Spinal Cord Injuries* (New York: Plenum Press, 1977), edited by Professor Marian Weiss, director of the internationally recognized Rehabilitation Clinic at Konstancin, Poland. Another significant study, funded in the NLM program in Israel, reviews current developments in family medical practice—Jack H. Medalie, editor, *Family Medicine—Principles and Applications* (Baltimore: The Williams and Wilkins Co., 1978).

Regional Resources and Biomedical Information

The PAHO Regional Library of Medicine (BIREME) continues as a model activity in serving as a regional biomedical and health information resource. Its extensive activities include exchange of materials,

reference services, interlibrary loans, computer-based information services from the MEDLARS data base and developing a library network.

About 16 percent of BIREME's annual budget is provided by PAHO's regular budget, 7 percent from WHO, and 77 percent from external sources including federal, state, and local governments of Brazil, and from philanthropic agencies. The staff of the Library has increased from 23 in 1969 to 71 in 1978. The most significant aspect of this increase is the addition of physicians and especially trained professional personnel. Since 1969, BIREME has performed 288,000 loan services; prepared 8,255 special bibliographies; and obtained and donated 309,000 journal issues to other Latin American libraries to strengthen their collections; and has provided specialized training to 324 Latin librarians.

Dr. Cummings, Director of NLM and chairman of the scientific advisory committee for BIREME, attended the tenth meeting of the committee in Sao Paulo, Brazil. The committee reviewed both policy considerations and the operational status of BIREME.

The Pahlavi Library of Medicine, established in Tehran, Iran, in 1975, has recruited and trained additional staff. It has also initiated an audiovisual program to assist the health community and has increased its specialized staff. In January 1978 the World Health Organization (WHO) designated the Pahlavi Library of Medicine as a WHO Regional Center for providing biomedical information services to the WHO eastern Mediterranean region.

Cooperation is being initiated between the World Health Organization's advisory committee on medical research and the National Library of Medicine. The National Library of Medicine will produce a specialized recurring bibliography in those tropical diseases selected by WHO for primary emphasis. The Pahlavi Library of Medicine will print it and the WHO will distribute approximately 10,000 copies. This model activity, when tested, may serve as a basis for developing further specialized information services and products significant for developing countries.

Visitors and Specialized Training

NLM receives about 1,000 international visitors annually. During FY 1978 these individuals represented 49 countries and many interests, such as medical research and education, health care, information and library science, administration and development of biomedical and health information programs, and construction of new library buildings.

Formal delegations from Japan included representatives of the Ministry of Health and Welfare, the Diet Library, and computer and information organizations. Groups of librarians came from Brazil, Spain, Germany and Colombia. Delegations from Italy were from the Ministry of Health and the National Federation of Medicine, which included the Chief of the Cabinet of the Ministry of Health, members of the Italian

Parliament, and physicians. Australian visitors have included Senator Davidson; Mr. K.W. Edmondson, secretary of the National Health and Medical Research Council; Mr. J.G. Burt, the assistant director general, Department of Health; Dr. G.N. Lance, the chief research scientist, Commonwealth Scientific and Industrial Research Organization; and, from the National Library of Australia, Mr. Bryan Yates, the deputy director; Mr. A. Ellis, the assistant director general for Networks and Coordination; and Mr. T. Barley, the chief of computer systems.

NLM also assists other agencies in receiving and preparing programs for information specialists from other countries.

In connection with NLM's bilateral MEDLARS agreements, NLM has received a number of individuals for specialized programs. They include: George Milligan of the Institute for Medical Literature, South African Medical Research Council, for training in indexing medical literature and searching the various NLM data bases; Fahimeh Shafaie of the Pahlavi Library of Medicine in Iran for training in audiovisuals; Dr. Cesar Macias of the National Center for Information and Documentation in Health of the Ministry of Health, Mexico, for advanced training as a search analyst; and Caterina Vollono of the Istituto Superiore di Sanita in Rome, Italy, for training in searching the various NLM data bases.

The NLM does not have, nor does it fund, a formal program for trainees from abroad. It does, however, try to respond to special requests from other governments or institutions where a person's experience qualifies him for specialized training which can be applied upon his return home. Some of those in such programs were: Pompeye Garcia, director of the National Medical Library in Cuba; Daisy de Valle, director of the department of information development of the National Information Center for Medical Sciences, Ministry of Public Health, Cuba; Dr.med. Oystein Wendelbo, deputy librarian, University Library of Bergen, Norway; and Dr. Reinhard Bradler from the German State Library, Berlin, East Germany.

In June, Miss Mary E. Corning, NLM, served as a consultant to the Subcommittee on Health Manpower and Medical Education of the U.S.-Egyptian Working Group on Health during the latter's meetings in Egypt. She also reviewed with the World Health Organization Regional Office in Alexandria the Egyptian medical library scene, WHO's designation of the Pahlavi Library of Medicine in Iran as a WHO Regional Library, WHO's plans for developing a medical library network in the region, and WHO's planned health information system.

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